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REVISTA DE MEDICINĂ MILITARĂ

- *Non-alcoholic Steatohepatitis Diagnosis and Treatment – Current Concepts*
- *Functional Evaluation and Neuro-Muscle-Skeletal Recovery in Lyme Disease: A Study on Motor Control Theories and Rehabilitation*
- *Multinodular and Vacuolating Neuronal Tumor – Challenges and Perspectives*
- *Navigating Cancer: Mental Adjustment as Predictor of Somatic Symptoms in Romanian Patients – A Cross-Sectional Study*
- *The Neurocardiogenic Impact of Ischemic Stroke: Intricacies of Cardiac Enzymes and the Vegetative System*
- *Radiotherapy and Reconstructive Surgery: Challenges, Implications, and Optimized Therapeutic Approaches*
- *Multidrug-resistant ESKAPE Pathogens in a Romanian Secondary-Care Hospital during the COVID-19 Pandemic*
- *Impact of Physical Performance on Haemodynamic and Cognitive Status in Romanian Older Adults*
- *Case Management of Delirium in Patients with Major Neurocognitive Disorders*
- *Gender-Dependent Associations Between Digit Ratio and Genetic Polymorphisms, BMI, and Reproductive Factors*

CLARIVATE ANALYTICS
EMERGING SOURCES CITATION INDEX
INDEXED

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Contents

Ana M. Ijacu, Laura G. Gagiu, Iulia M. Staicu, Corina Zugravu, Ciprian Constantin
● ***Non-alcoholic Steatohepatitis Diagnosis and Treatment – Current Concepts*** **3**

Marian Mitrica, Octavian Vasiliu, Andreea Plesa, Octavian M. Sirbu
● ***Multinodular and Vacuolating Neuronal Tumor – Challenges and Perspectives*** **10**

Daniela Schor, Vladimir Schor, Ramona Pavel, Pia S. Fagaras, Lucian G. Eftimie, Adina Geambasu, Mircea Bratu, Silvia Stroescu, Remus R. Glogojeanu
● ***Functional Evaluation and Neuro-Muscle-Skeletal Recovery in Lyme Disease: A Study on Motor Control Theories and Rehabilitation*** **17**

Monica Licu, Dragos M. Popescu, Claudiu G. Ionescu, Oana Voinea, Lidia Stoica, Adriana Cotel
● ***Navigating Cancer: Mental Adjustment as Predictor of Somatic Symptoms in Romanian Patients – A Cross-Sectional Study*** **27**

Maria M. Manea, Dorin Dragos, Maria I. Ghenu, Iulia I. Enache, Iulia C. Stoican, Cristina Ciulavu, Octavian Vasiliu, Carmen A. Sirbu, Sorin Tuta
● ***The Neurocardiogenic Impact of Ischemic Stroke: Intricacies of Cardiac Enzymes and the Vegetative System*** **36**

Flavia F. Lita, Andreea Grosu-Bularda, Florin V. Hodea, Andrei Cretu, Eliza M. Bordeanu-Diaconescu, Catalina S. Dumitru, Rheea M. Lita, Raducu A. Costache, Bogdan M. Marinescu, Ioan Lascar
● ***Radiotherapy and Reconstructive Surgery: Challenges, Implications, and Optimized Therapeutic Approaches*** **43**

Constantin M. Vlase, Alina V. Iancu, Claudia S. Stefan, Iulia Draghiev, Caterina N. Dumitru, Adrian Nistor, Manuela Arbune
● ***Multidrug-resistant ESKAPE Pathogens in a Romanian Secondary-Care Hospital during the COVID-19 Pandemic*** **51**

Justin Aurelian, Andreea Zamfirescu, Sorina M. Aurelian, Ruxandra Mihalache, Monica S. Gîdei, Costina D. Gîță, Ana G. Prada, Traian Constantin, Mirela Nedelescu, Corina Oancea
● ***Impact of Physical Performance on Haemodynamic and Cognitive Status in Romanian Older Adults*** **60**

Octavian Vasiliu, Cristina A. Panea, Andrei G. Mangalagiu, Bogdan M. Petrescu, Cristian A. Cândea, Maria M. Manea, Adela M. Ciobanu, Carmen A. Sîrbu, Marian Mitrică
● ***Case Management of Delirium in Patients with Major Neurocognitive Disorders*** **67**

Silvia Nica, Robert Sionel, Roxana Măciucă, Ortansa Csutak, Dănuț Cimponeriu, Mihai L. Ciobica, Matei I. Nica, Iuliana Chelu, Irina Radu, Mihai Toma
● ***Gender-Dependent Associations Between Digit Ratio and Genetic Polymorphisms, BMI, and Reproductive Factors*** **78**

Guidelines for authors **87**

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REVIEW

Non-alcoholic Steatohepatitis Diagnosis and Treatment – Current Concepts

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Abstract: NAFLD (Non-alcoholic fatty liver disease) is a condition of high importance due to its increased prevalence, estimated at 24% of the global population, and its potential progression to advanced liver disease, cirrhosis, and hepatocellular carcinoma. One-quarter of NAFLD patients have NASH (non-alcoholic steatohepatitis), which is histologically described as liver steatosis, inflammation, fibrosis, hepatocyte injury, and death. Metabolic disruptions, such as obesity, diabetes, and dyslipidemia, are considered to have a great impact on the development of NASH. Patients may have NAFLD for a long time before progressing into NASH, which highlights the necessity of periodic imaging and biochemical evaluation of the liver, and also presents an optimal window of therapeutic intervention. The challenge in developing treatment for NASH stems from the slow progression of the disease and the reliance on sequential biopsies as the diagnostic and staging tools. Several non-invasive tests have been developed as potential future alternatives to the current invasive gold standard. This review aims to assess the current available methods of diagnosis and treatment targeting inflammation.

Keywords: NAFLD; NASH; MASH; liver steatosis; liver fibrosis; metabolic syndrome; lanifibranor; obeticholic acid; semaglutide

INTRODUCTION

Non-alcoholic steatohepatitis (NASH) is an advanced form of non-alcoholic fatty liver disease (NAFLD), characterized by liver inflammation and hepatocyte injury, that is progressively evolving due to the accumulation of fat in the liver [1]. NAFLD results from an unhealthy diet and sedentary lifestyle, without high alcohol consumption, and is usually a silent disease before the advanced stages, including cirrhosis, liver failure, and hepatocellular carcinoma [2].

The highest rates of NAFLD were reported in the Middle East (32%) and South America (31%), followed by Asia (27%), USA (24%) and Europe (23%), whereas the lowest rates were in Africa (14%) [3-5]. It is estimated that 25% of the patients with NAFLD are thought to have NASH and a quarter of them are diagnosed with cirrhosis [3-5].

Recent studies show the association between metabolic disruptions and NASH, which is why a new medical terminology has emerged introducing the term MASH as metabolic-associated steatohepatitis. A bidirectional correlation exists between NAFLD and metabolic syndrome (obesity, insulin resistance, and dyslipidemia). Also, patients with type 2 diabetes mellitus (T2DM) have a greater risk of developing NAFLD, with a prevalence estimated at 57.80% (95%CI: 53.88% - 61.62%) [6]. NASH has been reported in 65.26% (95% CI: 51.73%-76.71%) of the patients with type 2 diabetes mellitus, who underwent liver biopsy [6]. In a meta-analysis of more than 8.5 million people from 22 countries, the results show that 80% of the patients with NASH are overweight or obese, 72% have dyslipidemia, and 44% are diagnosed with type 2 diabetes mellitus [3].

The evolution of NASH is non-linear. Some patients progress to cirrhosis, and most of them develop cardiovascular disease, but some patients, even those with fibrosis, may spontaneously regress. Cardiovascular mortality is the most common cause of death in patients with NASH. In contrast, in the U.S., due to decompensated liver disease, NASH is among the top three indications for liver transplantation [6,7].

In a study on patients with liver cirrhosis, secondary to HCV infection or NASH, over 4 years, it was estimated that the annual cumulative risk of HCC (hepatocellular carcinoma) was 2.6% per year in patients with NASH cirrhosis compared with 4.0%

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per year in those with HCV cirrhosis [8]. These figures suggest that NASH carries a risk of developing HCC that rivals the risk in patients with HCV-cirrhosis. As such, patients with NASH cirrhosis should be closely monitored for HCC. The decrease in HCV-related transplantation due to the significant effect of the HCV therapies placed NASH and ALD (alcohol-related liver disease) as the most common etiologies of liver disease among liver transplant waiting list registrants without HCC, and NASH is becoming a leading indication in patients with HCC [9].

MATERIALS AND METHODS

This review aims to assess the currently available methods of diagnosis and treatment targeting liver inflammation and fibrosis, named NAFLD, NASH, or similar.

We have selected over 200 English, French, and Romanian studies highlighting information on diagnosing and treating these hepatic diagnoses. For the development of this review, we further selected the articles based on our inclusion criteria, consisting of diagnosis and treatment-focused articles and recently published articles to ensure the current advancements in the field.

Databases such as PubMed, Up-to-date, Medline, and NCBI were used to perform the search using keywords: NAFLD, NASH, liver steatosis, liver fibrosis, and metabolic syndrome. Exclusion criteria were imposed to select the papers, such as the article publication date not exceeding 20 years old, and the publications to be in English, French, and Romanian, addressing the diagnosis and treatment concepts for NASH.

RESULTS

Diagnosis

Identifying a person with NASH can be difficult because neither the diagnosis nor the severity of the liver fibrosis can be predicted based on the risk factors (obesity, insulin resistance, or hepatic steatosis) alone. Accurate fibrosis staging, through biopsy series, is important for diagnosis and mortality assessment. All-cause and liver-specific mortality appear to increase once the F2 fibrosis stage has developed [10]. The risk of liver disease death rises by a factor of 50 to 80 for patients with NASH who have F3/F4 fibrosis, as compared with those who have little or no fibrosis [11,12]. People at risk for NASH, such as overweight or obese patients with metabolic syndrome, elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and negative noninvasive results for other causes of liver disease, should undergo further testing. Also, patients with type 2 diabetes mellitus over the age of 45 years are likely to have advanced fibrosis and bad liver outcomes [5].

Before advanced testing for NASH, patients should be thoroughly examined to exclude other causes of steatosis and liver damage and to determine the presence of commonly associated comorbidities (obesity, dyslipidemia, insulin resistance, diabetes, sleep apnea, hypothyroidism, and polycystic ovary syndrome). Excessive alcohol consumption, steatogenic medications, high serum ferritin with increased iron saturation, and viral or autoimmune hepatitis should be excluded [7].

The liver biopsy is an invasive procedure, currently considered the gold standard for diagnosing and staging NASH. Numerous non-invasive methods of diagnosis based on serum markers and imaging tests have been investigated, but their performance is not comparable with the biopsy (Table 1). The need for non-invasive tests has been enhanced to develop new treatments for NASH. Various emerging diagnostic tools are presented in Table 1 [7,13-25].

MRI-PDFF [7,13] (Proton density fat fraction MRI) is the most accurate method of detecting steatosis, whereas MRE [7,14] (Magnetic resonance elastography) is the most accurate tool of staging liver disease, by the “stiffness’’ indirectly related to fibrosis. Although availability and costs are a major challenge for clinicians, combining these tests can provide a risk stratification in patients with NAFLD. Non-invasive serum markers include alanine aminotransferase levels, and circulating keratin18 fragment levels and there are also tests such as Fibrometer, microRNA panels, and lipidomic panels. In patients with ALT>70U/L, NASH ALT prediction testing was found to have a 50% sensitivity and 61% specificity [7,15]. Considering the prediction ability of the serum ALT, it should not be used for definitive diagnosis, staging, or evolution of the disease, but only to guide further testing. The NASH Test combines demographic characteristics (age, gender, and BMI), serum markers (ALT and lipids), and alpha-2 macroglobulin, ApoA1, and haptoglobin, with a sensitivity of 33% and a specificity of 94%, indicating that it has a good negative predictive value (NPV) [7,16]. The Fibrometer NAFLD (based on age, weight, fasting glucose, AST, ALT, ferritin, and platelet count) achieves reasonably good results for mild to moderate fibrosis. The positive predictive value (PPV) for correctly identifying F=1 was 84.9%, the NPV was 66.7% and the diagnostic accuracy was 80%. The PPV for F=3 was 74.5%, the NPV was 86.2% and the diagnostic accuracy was 82.1% [17-20]. Fibromax, a diagnostic tool composed of 4 non-invasive biomarker panels, can be used for the diagnosis of steatosis (estimated by the SteatoTest), necrosis and inflammation (evaluated by ActiTest and NashTest-2), and fibrosis (FibroTest). Although it is a well-validated and relatively frequently used test, it may not be accurate for patients with T2DM [21]. OWLiver (Overweight Liver) [16,18] is an alternative for overweight patients and PROC3 (Pro Collagen III) can be used as a differentiating test between steatosis and NASH [24]. NASH Index Score 4 (NIS4) [23] and Enhanced liver fibrosis (ELF) [25] are tools that exclude AST and ALT as parameters in the diagnosis process.

There are two main scoring systems for the biopsy results in NASH. The NAS (NAFLD Activity Score) sums the score of steatosis, lobular inflammation, and ballooning of the liver cells. The score (0-8) is not diagnostic. It was designed to evaluate the histological changes in seriate biopsies. It is usually interpreted by adding the fibrosis score (0-4) (Table 2) [7,26-27]. Another available score is SAF

(Steatosis, Activity, and Fibrosis). By evaluating 1000 biopsies, there was an excellent concordance between the two scores in determining the definite NASH, whereas 84% of the NAS borderline biopsies (3-4), were identified by SAF score as NASH [7,26-27].

Table 1: Non-invasive methods of diagnosis [7,13-25]

Test	Parameter measured	Observations
MRI-PDFF [7,13] (Proton density fat fraction magnetic resonance imaging)	steatosis	most accurate method of detecting steatosis
MRE [7,14] (Magnetic resonance elastography)	liver stiffness	most accurate modality of staging liver disease, by the ''stiffness'' indirectly related to fibrosis.
NASH Test [7,16]	age, sex, height, weight, serum triglycerides, cholesterol, a-macroglobulin, apolipoprotein A1, haptoglobin, gamma-glutamyl transpeptidase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin	sensitivity of 33% specificity of 94%
FibroMeter VCTE [17-20] (Vibration Controlled Transient Elastography)	Fibrosis, liver stiffness Combines TE (transient elastography) with biochemical markers (age, sex, AST, urea, platelets, prothrombin time, GGT, and alpha2-macroglobulin)	shows good results for mild to moderate fibrosis By combining biochemical markers with imagistic results it increases the accuracy
Fibromax [21]	Combines 4 non-invasive biomarker panels SteatoTest, ActiTest, NashTest-2, and FibroTest	affordable and simple score, but it may not be accurate for patients with T2DM
FNI [22] (The Fibrotic NASH Index)	fibrosis AST, high-density lipoprotein cholesterol, and hemoglobin A1c	accurate, affordable, and simple score for patients with fibrotic NASH
NIS4 [16,18,23] (NASH Index Score 4)	miR-34a-5p, alpha-2 macroglobulin, YKL-40, and glycated haemoglobin A1c	Identifies at-risk patients, defined as [NAS] ≥4 and fibrosis stage ≥2 on biopsy
OWLiver [16,18] (Overweight Liver)	extensive analyses of triglycerides panel by high-performance liquid chromatography and mass spectrometry	Used for individuals with BMI>25 kg/m^2
PROC3 [18,24] (Pro Collagen III)	Pro collagen III	Differentiates steatosis from NASH
ELF [18,25] (Enhanced liver fibrosis)	fibrosis hyaluronic acid, procollagen III, and tissue inhibitor of matrix metalloproteinase 1 (TIMP-1)	stages liver fibrosis independently of AST, ALT elevations

Treatment

The main pathogenic processes identified in NASH are metabolic stress, inflammation, and fibrosis. Pharmacologic agents that target these key mechanisms are being investigated in clinical trials [2].

Due to the lack of pharmacological therapies for NASH, lifestyle modifications remain the main intervention for mitigating histological impairment. Weight loss appears to bring the highest benefit.

Usually, the recommendations include 5-10% weight reduction for obese and overweight patients, physical activity, and a Mediterranean diet. Ultra-processed foods and drinks, fructose-enriched beverages, and alcohol should be avoided. In addition, associated comorbidities (T2DM, dyslipidemia, POS) should be treated [1,26].

Vitamin E, pioglitazone, and statins are available options for patients with NASH. Studies have indicated the role of vitamin E in the reduction of steatosis and fibrosis [28,29]. Pioglitazone, a treatment used for type 2 diabetes mellitus, has been reported to significantly reduce fibrosis in NASH patients. In addition, statins have been tested on NAFLD/NASH patients, with substantial results in improving steatosis and fibrosis [30].

The PIVENS trial focused on NASH patients without diabetes, who were randomly assigned to one of three groups (pioglitazone 30 mg daily, vitamin E 800 IU daily, or placebo). The vitamin E group had a significantly higher rate of histology improvement than the placebo group 43% vs. 19%, but pioglitazone did not meet the primary outcome [31]. Based on several studies, there is a variability in treatment response for vitamin E supplementation. Genetic variations in haptoglobin and FADS1/FADS2 (fatty acid desaturase 1 and 2) have been suggested to interfere with the treatment response, determining whether a patient will show histological improvement or not [32].

Many new potential therapies for NASH are currently studied in phase III trials. The pan-PPAR agonist (Peroxisome proliferator-activated receptors), lanifibranor, has completed the phase IIb trial with 247 participants, the results show a reduction in the SAF activity score (> 2 points), with no increase in fibrosis, achieved by 49% of patients compared with 27% on placebo. The results were significantly higher among those who received 1200 mg of lanifibranor vs. the group with 800 mg dose. In the lanifibranor groups, there was an improvement in liver enzyme levels and also in the majority of lipid, inflammatory, and fibrosis biomarkers [33]. There is an ongoing phase 3 study conducted to evaluate the safety and efficacy of lanifibranor compared to placebo on 1000 participants

with NASH and liver fibrosis histological stage F2 or F3 [34].

The GLP-1 receptor agonist, semaglutide, has also completed a 72-week, phase 2 trial (NN9931-4296) with 320 participants, showing resolution of NASH and no worsening of fibrosis for 59% of patients, in the 0.4mg group, and 40% of patients, in the 0.1mg group, compared with 17% on placebo. The percentage of participants with an improvement in NAS score was 82.9% in the 0.4mg group compared with 43.8% on placebo [35]. A phase 3 study, ESSENCE (The Effect of Semaglutide in Subjects With Non-cirrhotic Non-alcoholic Steatohepatitis), was initiated in 2021 and the interim results are expected in 2024 [36].

Table 2: NAS score and fibrosis staging (adapted from [7,27])

Characteristic	Score
Steatosis	<5%=0 5-33%=1 (mild) 33%-66%=2 (moderate) >66%=3 (severe)
Lobular inflammation	No foci = 0 <2 foci per 200 field =1 2-4 foci per 200 field =2 >4 foci per 200 field = 3
Ballooning	None = 0 Few = 1 Many cells = 2
NAS Score	0-8
Fibrosis	None = 0 Mild = perisinusoidal or periportal (stage 1) Moderate = perisinusoidal and portal/periportal (stage 2) Severe = bridging fibrosis (stage 3) Cirrhosis = stage 4

For liraglutide, also a GLP-1 analog, a multicenter, double-blinded, randomized, placebo-controlled phase 2 trial (the LEAN trial) has demonstrated histological resolution of non-alcoholic steatohepatitis and a significant effect on liver fibrosis after 48 weeks of treatment. In addition, the comparison between pioglitazone and liraglutide showed better results for the latter [37-39].

Obeticholic acid, a selective FXR (farnesoid X receptor) agonist, approved by the FDA in 2016 for primary biliary cholangitis, previously completed a phase III trial (REGENERATE) on 1968 NASH participants with fibrosis F2–F3. The results show that the drug improved the fibrosis score by at least one stage, but did not meet the endpoint of NASH resolution [40]. The FDA rejected the approval of obeticholic acid for NASH in May 2023, based on the modest benefits that did not outweigh the risks.

A phase IIb randomized study of the efficacy and safety of Namodenoson, an A3 adenosine receptor (A3AR) agonist, in the treatment of NASH is ongoing. Previous trials on Namodenoson showed normalization in ALT and AST levels after 12 weeks of treatment [41].

Pegozafermin, a long-acting glycopegylated fibroblast growth factor 21 (FGF21) analog, showed improvements in fibrosis in a phase 2b trial (ENLIVEN). The fibrosis improvements occurred in 7% of the placebo group and between 22-27% in the pegozafermin groups (22% with 15 mg – pegozafermin, 26% on 30 mg dosage, and 27% on 44 mg dosage). The NASH resolution was 2% in the placebo group, 37% in the 15mg pegozafermin group, 23% in the 30 mg pegozafermin group, and 26% in the 44 mg pegozafermin group. The study completion date is estimated around September 2024, demonstrating favorable prospects for advancing to phase 3 [42,43].

Oxidative stress and the formation of reactive oxygen species (ROS) are often associated with the progression of NAFLD to NASH. Excessive ROS formation impairs insulin sensitivity and inflammatory responses. The release of pro-inflammatory molecules and uncontrolled ROS production in many cells is partially the result of TAGE (toxic advanced glycation end-products) and receptor for AGEs (RAGE) interactions [44,45]. Hyperglycemia contributes to the production of advanced glycation end-products (AGEs), especially AGEs formed from glyceraldehyde (GA), which are highly cytotoxic, damaging the hepatocytes. AGEs and TAGE were measured in a study of 66 patients with histologically confirmed NASH without cirrhosis, 10 with NAFL, and 30 control subjects [46]. The TAGE levels of NASH patients were significantly higher than those with NAFL. Ultra-processed foods with a high content of sugar (fructose-enriched or sugar-sweetened drinks) and dietary AGEs have been suggested to contribute to the development of obesity, metabolic syndrome, and the progression of NAFLD/NASH when consumed excessively [47].

Antioxidants such as pentoxifylline (PTX), silybin, resveratrol, and vitamins A, C, and E are used in clinical trials against NAFLD and NASH [47].

PTX treatment with three divided doses of 400 mg for one year improved hepatic histological activity. NAS ≥ 2 improved by (75%) in the PTX group and 30% in the placebo group, but there was no impact on fibrosis [48]. Also, another study on PTX (1200 mg/day) and fenofibrate showed a beneficial effect on indirect biochemical markers of hepatic fibrosis. After 24 weeks, the association of fenofibrate and PTX resulted in reduced liver fibrosis and stiffness, insulin resistance, and inflammation [49]. The combined administration of PTX (1200 mg/daily) and metformin (1500 mg/ daily) for six months reduced AST, and ALT levels and improved

insulin resistance in patients with NASH [50]. A meta-analysis based on 5 RCT on patients with NAFLD/NASH reported that PTX treatment could reduce glucose serum levels, liver transaminases, body weight, and TNF-α levels and also improve NAS and fibrosis scores [51]. Another study used combinational therapy (PTX+Vitamin E) and the results showed regression of fibrosis compared to vitamin E alone [52]. In a phase 2 study, pentoxifylline (PTX) alone significantly improved steatosis, lobular inflammation, and liver fibrosis and was well tolerated [53]. Therefore, PTX can be used along with other drugs as an adjuvant for metabolic diseases.

A phase 4 study conducted on 102 NASH patients divided into 3 intervention groups (PTX, vitamin E, and ursodeoxycholic acid) measured the levels of several serum markers (AST, ALT, IL6, and CCL2/ MPC-1, albumin, total bilirubin, direct bilirubin, total cholesterol, triglyceride, LDL, HDL) for 3 months [54].

In 2017 a study [55] based on an experimental rat model of NASH demonstrated for the first time that the combination of SAMe (S-Adenosyl-L-Methionine) and DLPC (Dilinoleoylphos-phatidylcholine), two physiologic antioxidants, significantly opposed liver injury generated by fat excess.

Numerous studies on hepatoprotective drugs, probiotics, and antioxidants, such as Siliphos—Selenium—Methionine—Alpha Lipoic Acid, omega-3 fatty acids, and vitamins A, C, and E, are currently ongoing [47,52,56-58].

CONCLUSION

The treatment for non-alcoholic steatohepatitis is, unfortunately, an unmet need. At present, there are no FDA-approved therapies for this condition, and the same holds for the EU. Considering the increasing prevalence and the risk for progression toward advanced liver disease, cirrhosis, and hepatocellular carcinoma, there is a major demand for reliable non-invasive biomarkers and specific therapy. In addition to healthy diet and exercise, many new pharmacological agents, such as lanifibranor, semaglutide, and obeticholic acid are being studied. Antioxidants as well are used in clinical trials against NAFLD and NASH.

Despite the clinical and epidemiological significance, the accurate diagnosis, monitoring of the diagnosed patients, and available licensed treatments remain the challenges of NASH.

Conflicts of interest and sources of funding

The authors declare no conflict of interest.

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Authors' contribution

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REVIEW

Multinodular and Vacuolating Neuronal Tumor – Challenges and Perspectives

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Abstract: A multinodular and vacuolating neuronal tumor (MVNT) is a rare non-malign central nervous system tumor. The cerebral cortex of young to middle-aged adults is affected and seizures and focal neurological deficits could reveal it. Despite being considered a low-grade tumor, MVNT can be challenging to diagnose and manage due to its histopathological similarities to other neuronal tumors. The limited number of reported cases makes it difficult to establish definitive guidelines for treatment and follow-up. Given the relatively recent discovery of MVNT, there is a need for further research to better understand its pathogenesis, optimal treatment and long-term strategies. Furthermore, studying MVNT can contribute to the broader understanding of brain tumor biology and the intricacies of tumor heterogeneity. This paper explores the challenges and perspectives surrounding MVNT to improve clinical decision-making and patient outcomes. Based on the present narrative review, advancements in diagnostic technologies have shown promise in addressing the challenges associated with diagnosing MVNTs. Liquid biopsy is an innovative and non-invasive diagnostic tool that analyzes biomarkers to provide information about tumors, and radiomics is a method that extracts quantitative data from medical images to provide detailed insights into tumor characteristics. Such innovative diagnostic technologies are important because they have the potential to significantly improve the current diagnostic landscape for MVNTs, allowing for earlier detection, accurate classification, and personalized treatment strategies.

Keywords: multinodular and vacuolating neuronal tumor; radiomics; liquid biopsy; diagnostic methods; histological examination; FDG-PET/CT; immunohistochemistry

INTRODUCTION

First described in 2013, multinodular and vacuolating neuronal tumor (MVNT) was classified as a benign ganglion cell grade I tumor, potentially associated with seizures, with a specific molecular marker, as outlined in the WHO 2016 and 2021 classification [1-3]. The discovery of MVNT is often accidental, and it is frequently asymptomatic [1,2]. Studying MVNT is of utmost significance in neuro-oncology. Understanding the molecular mechanisms underlying the development and progression of MVNT can provide insights into potential therapeutic targets and treatment strategies.

Typically identified in adults, MVNTs seem to appear during neurogenesis and present as subcortical clusters of nodular lesions within the cortex and superficial subcortical white matter [4]. Structure abnormalities in the cortex may be present with it [4,5]. Initially classified as either neoplastic or malformation, recent research on MVNTs emphasizes their stable nature over time, suggesting that they are "leave me alone" lesions with minimal changes in volume, thus underscoring the potential for less frequent imaging surveillance [6,7]. Whether the nodules of vacuolar neurons are a definite neoplastic transformation or aberrant development is still up for debate [6]. Overall, these insights contribute to a nuanced understanding of MVNTs, highlighting the complexities and diagnostic considerations surrounding these distinct neuronal tumors. Moreover, the purpose of this research is to shed light on the challenges and perspectives surrounding MVNT.

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MATERIALS AND METHODS

A narrative review was conducted through five electronic databases (PubMed, CINAHL, Google Scholar, Cochrane, Web of Science/Clarivate), using as keywords "multinodular and vacuolating neuronal tumor" AND "diagnosis" OR "pathogen*" OR "imaging" OR "treatment". All primary and secondary reports found from the inception of the respective databases up to July 2024 were explored for relevant data. Only papers that addressed explicitly the pathogenesis, diagnosis methods,

and treatment strategies of MVNT were included in the secondary analysis**.**

RESULTS

Based on the literature search, 34 primary and secondary reports were reviewed in detail. The results were classified according to the three areas of interest, i.e., (1) pathogenesis and classification of MVNT, (2) imaging characteristics, and (3) diagnosis and treatment.

Classification and pathogenic characteristics of MVNT

Recent studies have highlighted the challenge of defining and classifying MVNT. Due to its rarity and unique histopathological features, there is ongoing debate within the scientific community regarding its precise definition and classification. Some researchers argue that MVNT should be considered a separate entity from other neuronal tumors due to its distinct morphological characteristics and clinical behavior. On the other hand, some propose classifying it under the umbrella of neuronal and mixed neuronal-glial tumors based on its neurocytic differentiation and immunohistochemical profile.

The purely neuronal tumors in the 2021 WHO classification include multinodular and vacuolating neuronal tumors, gangliocytoma, extraventricular neurocytoma, central neurocytoma, dysplastic cerebellar gangliocytoma, and cerebellar liponeurocytoma.

The mixed glioneuronal tumors include dysembryoplastic neuroepithelial tumor, diffuse glioneuronal tumor with oligodendroglioma-like features and nuclear clusters, ganglioglioma, desmoplastic infantile ganglioglioma/astrocytoma, papillary glioneuronal tumor, rosette-forming glioneuronal tumor, myxoid glioneuronal tumor, and diffuse leptomeningeal glioneuronal tumor [13].

There is a consensus on the need for standardized diagnostic criteria to identify and classify MVNT cases accurately. This would facilitate better communication among pathologists and clinicians, improving management strategies and outcomes for patients with MVNT.

The WHO 2016 classification defines MVNT as a benign ganglion cell tumor with specific pathologic hallmarks [2]. These nodular lesions are typically located in specific brain regions and can present differently across age groups, emphasizing the importance of histopathological examination for accurate diagnosis [1,14,15].

Histopathological analysis of MVNT reveals several distinctive features that aid in their diagnosis and differentiation from other neuronal tumors. One of the hallmark features of MVNT is the presence of numerous vacuoles within the tumor cells. This vacuolation can create a “floating” appearance of the cells and is a critical diagnostic criterion. MVNT typically exhibits a multinodular architecture. The tumor forms distinct nodules, which may vary in size, often surrounded by a gliotic background. Such detailed histopathological analyses are essential for elucidating the distinct features of MVNT and guiding effective clinical management strategies. Nevertheless, no histopathological evidence is available to confirm the diagnosis since only a small percentage of patients with suspected MVNT undergo surgery [10].

Immunohistochemical markers play a crucial role in the diagnosis and classification of MVNT. Various markers have been studied, differentiating MVNT from other tumors with similar histological features, such as dysembryoplastic neuroepithelial tumor (DNT) or ganglioglioma [16,17]. So, immunohistochemistry (IHC) is a crucial tool in the diagnosis and characterization of MVNT, establishing the neuronal nature of MVNT, as seen with positive staining for neuronal markers [18]. MVNT typically shows positivity for several neuronal differentiation markers: NeuN, a neuronal nuclear antigen typically expressed in mature neurons, β-III tubulin, which is highly expressed in neuronal cells and can help confirm the tumor’s neuronal lineage. Synaptophysin, a protein associated with synaptic vesicles, indicates neuroendocrine differentiation and is often used to demonstrate the presence of neurons. Although MVNT is primarily neuronal, some glial markers may also be expressed, reflecting maybe the mixed composition of the tumor. GFAP (Glial Fibrillary Acidic Protein) positivity can indicate a glial component in the tumor. Phenotypic analyses may also include checking for markers that indicate low proliferation rates, which can help distinguish MVNT from more aggressive tumors. Markers like Ki-67 are occasionally assessed but typically show low proliferation in MVNT. The absence of expression for markers associated with high-grade tumors, such as p53 or other markers linked to aggressive histology, reinforces its benign nature [18,19].

Understanding the molecular pathogenesis of Multinodular Vacuolating Neuronal Tumors (MVNT) presents a significant challenge due to the tumor’s unique histological features and clinical behavior. MVNTs are characterized by vacuolated tumor nodules with glial and neuronal differentiation, primarily affecting the cerebrum in adults. The pathognomonic radiological features, such as the soap-bubble morphology and lack of enhancement post-gadolinium injections, provide important clues for differential diagnosis and management strategies [4,11,20,21]. The molecular mechanisms driving its formation and growth remain elusive. Further research is warranted to elucidate the genetic alterations and signaling pathways involved in the development of MVNT. The MAP (Mitogen-Activated Protein) kinase signaling pathway is a critical cellular signaling pathway that regulates various cellular processes, such as growth, proliferation, differentiation, survival, and apoptosis. This pathway is activated by various extracellular signals, including growth factors, cytokines, and environmental stresses. MAP kinase signaling pathway possibly sheds light on targeted therapeutic approaches [22].

Research has identified specific genetic mutations that may contribute to the development of MVNTs. For instance, missense mutations in the BRAF gene or HRAS gene have been linked to the pathogenesis of tumors [22,23]. Vacuolization and neuronal differentiation in MVNTs are characterized by vacuolated neurons. This cellular morphology suggests that disruptions in normal

neuronal differentiation and cellular homeostasis may be due to genetic and epigenetic factors. Investigating the presence of other oncogenes and tumor suppressor genes may provide further insights. In exploring the molecular underpinnings of MVNT, a deeper understanding of its pathogenesis may pave the way for personalized treatment strategies and improved patient outcomes in the future. Like many tumors, MVNTs may exhibit altered vascularization patterns [24]. The tumor microenvironment, including the interaction between tumor cells and surrounding glial cells, immune cells, and extracellular matrix components, plays a crucial role in tumorigenesis [25,26]. Studying these interactions can show how the tumor ecosystem supports MVNT growth and survival.

Table 1: Multinodular and vacuolating neuronal tumor (MVNT) characteristics

Characteristics	Descriptors
Definition [2,3]	Low-grade tumors (grade I) comprising monomorphous neuronal elements in discrete and coalescent nodules, with vacuolar changes both in tumor cells and the neuropil, with a molecular pattern impaling MAPK pathway
Localization [4,9,10]	Parietal lobe, frontal lobe, temporal lobe, occipital lobe, spinal, rare cases of multiple localization, mainly subcortical white matter rare cases with cortical extension
Imaging features [4,11,12]	**Brain CT**- is usually normal or shows a non-enhancing/non-calcifying cortical/subcortical white-matter hypodense lesion, absence of mass effect and edema; **Brain MRI** – intra-axial multiple clustered nodules hyperintense on T2WI and FLAIR; T1WI: small hypointense, homogeneous, and well-defined nodules, some clustered tightly or with a small interface between them, located at the cortical-subcortical junctional side; Abnormal white matter signal surrounding the bubble-like or bunch of grape appearances lesions; No contrast enhancement; Restricted diffusion could be present with high ADC values rare **FDG-PET/CT** brain imaging showed tumor hypometabolism
Histological examination [4,8,12]	No evidence of mitosis, necrosis, or microvessel proliferation; Abnormal clusters and numerous vacuoles within the tumor cells, with different sizes, often surrounded by gliotic tissue; Glioneuronal hamartomas; Hypomyelinated plaque-like nodules extending into the deep cortex;
Immunohistochemical stains [4,8]	Many neuronal cells show weak immunoreactivity for synaptophysin and negative immunoreactivity for neuronal nuclear and neurofilament proteins; Variable background of positive dendritic staining for CD34; Negative for IDH1-R132H mutation antibody; Staining was normal for ATRX and p53; The Ki67 proliferation refraction was very low; GFAP highlighted the reactive astrocytes within the nodules; The vacuolated cells were immunoreactive for synaptophysin, while the fibrillary tumor matrix showed decreased synaptophysin expression compared to the adjacent cortex
Natural evolution [4]	Stable on time, „leave me alone" tumor

MAPK- Mitogen-Activated Protein Kinase; CT – computer tomography; MRI- magnetic resonance imaging; T2 FLAIR – space inversion recovery with fluid attenuation; FDG-PET/CT- fluorodeoxyglucose positron emission tomography/computed tomography; CD34 - transmembrane phosphoglycoprotein encoded by the CD34 gene; IDH1- isocitrate dehydrogenase; ATRX- chromatin remodeling · nucleosome assembly; p53- tumor suppressor gene; Ki67 – a nuclear nonhistone protein present in all active phases of cell cycle; GFAP – Glial fibrillary acidic protein responsible for astroglial cytoskeleton and is not found outside the CNS

Imaging Characteristics of MVNT

Imaging characteristics of MVNT reveal distinctive features that aid in their diagnosis and differentiation from other brain tumors. Described as low-grade lesions primarily found in the cerebrum, MVNT presents as clustered multinodular structures within the cortex and subcortical regions (Table 1). The brain MRI revealed multinodular T2-hyperintense lesions in both the deep cortex and superficial white matter of the frontal lobes or temporal lobes, exhibit a unique soap-bubble morphology, hyperintensity on T2 FLAIR sequences, and minimal or absent contrast enhancement [10,16,27]. Based on the signals from T1, T2, and T2 FLAIR, the nodules have nonhomogeneous signal intensity due to low T1, high T2, and low FLAIR vacuole aspects. Confluent T2/FLAIR hyperintensity overlying cortex was present in some cases [4]. The larger nodules have an inner core that is hypointense, a rim that is hyperintense, and areas with a high signal intensity that connect the nodules. The smaller nodules exhibit a signal intensity that is not uniform, with a central dot of low-intensity [11]. The nodules' periphery shows high signal intensity on FLAIR because of high protein content and neuronal demyelination [11].

Sometimes MR spectroscopy indicates an increase in the choline peak and a decrease in the N-acetyl aspartate peak, and tractography shows a partial disruption of the typical structure caused by the absence of lesional cortical layers [11,28]. No increase in perfusion was observed by perfusion-weighted imaging in another study, and abnormal peaks were not detected by MR spectroscopy [10]. Despite their benign nature, the pathologic hallmark of MVNT, questions their neoplastic or malformative origin and potential association with seizures [29]. Cases of a spinal cord lesion resembling cerebral MVNT of unknown significance were named MVNT-like spinal cord lesions. With intramedullary cystic ovoid nodules within the white matter, some immediately contiguous to the grey matter, this lesion was stable in a follow-up [9,30]. The presence of well-delineated intramedullary cystic ovoid nodules within the spinal cord raises questions about the underlying pathophysiology of MVNT [9]. A comprehensive MR protocol has been suggested to

increase the diagnostic confidence of MVNT [10].

Diagnostic and treatment of MVNT

Despite advancements in imaging and molecular techniques, MVNT can present with various clinical manifestations, posing diagnostic challenges. Usually, MVNT is revealed as an incidentaloma [31]. The clinical presentation is nonspecific, with symptoms such as seizures, headaches, or focal neurological deficits, often mimicking other more common brain tumors or epilepsy syndromes [1,14]. Additionally, the radiological features of MVNT on MRI can be subtle and easily overlooked, leading to misdiagnosis. The lack of specific diagnostic criteria for MVNT further complicates accurate identification, underscoring the need for histopathological examination for definitive diagnosis [16,32]. Biopsy remains the gold standard for confirming MVNT, highlighting the importance of integrating clinical, radiological, and pathological findings to navigate the diagnostic challenges posed by this rare entity in neuro-oncology. Additionally, the classification of MVNT as a benign neuronal tumor, possibly associated with seizures, further complicates the understanding of its neurological manifestations, especially in young patients [33].

Table 2: Immunohistochemical analysis [8,19]

Neuronal markers		Glial markers	
NeuN (Neuronal Nuclei)	A marker for neurons, specifically in post-mitotic neurons. It is widely used to identify neuronal populations in various brain regions.	GFAP (Glial Fibrillary Acidic Protein)	A specific marker for astrocytes. Increased expression is often seen in reactive astrocytes following injury
MAP2 (Microtubule-Associated Protein 2)	A neuron-specific protein that stabilizes microtubules and is important for dendritic structure.	Olig2	A transcription factor and marker for oligodendrocyte precursor cells and mature oligodendrocytes, essential for myelination in the central nervous system
βIII-Tubulin (Tuj1)	A marker commonly used to identify neurons, particularly in developmental studies.	S100	A protein found in astrocytes, used for identifying glial cells
Synaptophysin	A presynaptic vesicle protein, often used to identify synaptic structures and neuronal activity	CD68	A marker for microglia, reflecting macrophage activity in the central nervous system and often used in studies of neuroinflammation.

Distinguishing MVNT from entities such as dysembryoplastic neuroepithelial tumor (DNET), ganglioglioma, extraventricular neurocytoma, and low-grade glioma is sometimes challenging [34]. The bright diffusion sign and absence of cortical involvement could differentiate MVNT from DNET [35]. Moreover, incorporating genetic and molecular analyses can further aid in narrowing down the list of differential diagnoses and confirming the diagnosis of MVNT. Immunohistochemical analysis for neural and glial markers are also helpful (Table 2). Antibodies against neuronal protein HuC/HuD (HuC/HuD), pan-neurofilament (pan-NF), neurofilament 200 KD (NF200 KD), chromogranin, and antibodies against glial fibrillary acidic protein (GFAP), nestin, CD3, CD45, CD68, CD34, human leukocyte antigen-DR (HLA-DR), isocitrate dehydrogenase1 (IDH1), calbindin, parvalbumin, calretinin, Ankyrin-G, p62 and Ki67, BRAF(V600E) enhance diagnostic accuracy [8,19]. Immunopositivity for HuC/HuD and Olig2 proves that MVNT appears during neuronal development [4].

The latest WHO tumor brain classification has classified MVNTs as grade I, and the mitogen-activated protein kinase (MAPK) is considered a molecular marker [3,8]. The MAPK is a key signaling pathway that transmits signals from the cell surface to the nucleus and regulates various cellular processes, including growth, proliferation, differentiation, and survival. Further research in this area, particularly investigating specific diagnostic markers and biomarkers, is warranted to refine the differential diagnosis process for MVNT.

Factors such as tumor size, location, and the presence of associated neurologic deficits can influence treatment strategies and prognosis.

One of the foremost challenges in the preoperative diagnosis of MVNT is the difficulty in distinguishing them from other neoplastic or malformative lesions to avoid unnecessary surgical interventions [36]. The characteristic imaging features of MVNT, such as the subcortical nodular lesions with unique signal properties on MRI, can often be mistaken for more aggressive tumors due to their atypical presentation in younger patients. The rarity of MVNT in young individuals poses a diagnostic dilemma, questioning the

classification of these lesions as true neoplasms or malformative anomalies [22,31,21].

Imaging modalities and treatment strategies play pivotal roles in managing epileptic patients, especially those with drug-resistant epilepsy considered for neurosurgery. Utilizing advanced imaging techniques such as the Harmonized Neuroimaging of Epilepsy Structural Sequences (HARNESS-MRI) protocol and 7-Tesla MRI can aid in identifying previously occult epileptogenic lesions and improving surgical outcomes [37,38]. Additionally, the development of MRI postprocessing techniques and functional imaging modalities like EEG-functional MRI contribute to enhanced sensitivity in lesion detection and focus localization [39].

Surgery is often considered the primary treatment option for multinodular vacuolating neuronal tumors (MVNTs) under several circumstances. If the MVNT is causing neurological symptoms (such as seizures, headaches, or focal neurological deficits), surgical intervention may be necessary to alleviate these symptoms, when the tumor is accessible and can be safely resected without causing significant damage to surrounding brain tissue. Histological confirmation by surgical resection can provide a definitive diagnosis through the histopathological exam, which is crucial for confirming the nature of the tumor and ruling out other possible lesions. However, the precise location of the tumor within the brain can sometimes pose challenges in obtaining a biopsy sample. In such cases, advanced imaging techniques and neurosurgical expertise are indispensable in ensuring accurate sampling for an accurate diagnosis and subsequent management of MVNT. It is essential that surgical decisions are made in consultation with a team of specialists, including neurosurgeons and oncologists, who can evaluate the risks and benefits specific to each patient's condition and tumor characteristics. Functional MRI is as accurate as WADA testing, for determining language dominance [40].

The management of asymptomatic MVNT often involves careful observation rather than immediate intervention. However, a strategy of active surveillance can be appropriate for asymptomatic or minimally symptomatic MVNT. This involves regular follow-up through serial neurological examinations and imaging studies (usually MRI) every 6-12 months**.**

DISCUSSION

Advancements in diagnostic technologies have shown promise in addressing the challenges associated with diagnosing MVNTs. One emerging technology that holds potential is liquid biopsy, an innovative and non-invasive diagnostic tool that analyzes biomarkers (circulating tumor cells and genetic material) from bodily fluids (such as blood, urine, or cerebrospinal fluid) to provide information about tumors [41-46]. Circulating Tumor DNA (ctDNA) from the blood allows for the detection of genetic mutations and alterations associated with MVNT. Liquid biopsy is less invasive than traditional tissue biopsy, making it a more feasible option for patients, especially in complex cases where surgical options may be limited. It allows for repeated sampling without the risks associated with multiple surgical procedures, enabling ongoing monitoring.

Additionally, the development of radiomics, a method that extracts quantitative data from medical images to provide detailed insights into tumor characteristics, could aid in distinguishing MVNTs from other brain tumors with similar radiographic features [44-46]. These innovative diagnostic technologies have the potential to revolutionize the current diagnostic landscape for MVNTs, allowing for earlier detection, accurate classification, and personalized treatment strategies. Furthermore, integrating these technologies into clinical practice could improve patient outcomes and enhance our understanding of MVNT biology.

More studies are needed to elucidate the genetic mutations and molecular pathways involved in the development of MVNT. This would not only provide valuable insights into the underlying mechanisms of this rare brain tumor but also potentially identify novel therapeutic targets. Additionally, clinical research focusing on the efficacy of different monitoring modalities is crucial for optimizing patient outcomes**.**

CONCLUSION

Based on the results of this narrative review, emerging technologies allow for a re-conceptualization of the MVNT diagnosis and treatment. Although data regarding the validity of the new imaging and molecular techniques are still gathering, the fact that WHO includes MAPK as a marker for MVNT indicates the need for further refinement of the differential diagnosis based on molecular explorations in this pathology. The references in the literature related to genetic mutations and alterations associated with MVNT suggest new research directions congruent with the paradigm of personalized medicine.

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Authors' contribution

Conceptualization, M.M., O.V., and O.M.S.; methodology, O.V., A.P., and O.M.S.; software, M.M., A.P., and O.M.S.; validation, M.M., O.V., and A.P.; formal analysis, O.V.; investigation, M.M.; resources, A.P., and O.M.S.; data curation, O.V.; writing—original draft preparation, M.M., O.V., and O.M.S.; writing—review and editing, M.M., O.V., and O.M.S. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

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ARTICLE

Functional Evaluation and Neuro-Muscle-Skeletal Recovery in Lyme Disease: A Study on Motor Control Theories and Rehabilitation

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Abstract: Background: Patients with Lyme disease often suffer from neuro-motor sequelae following Borrelia infection, leading to impairments in balance, posture, and spinal musculoskeletal functionality. This study aims to evaluate the effectiveness of physical therapy in addressing these impairments. Methods: Initial assessments were conducted using the GPS Posture-test System to evaluate static bipodal balance and posture, and BACKFIX Technology for unipedal balance and spinal functionality. Disturbances in balance, postural asymmetries, and a forward-shifted center of gravity were observed. The patient then underwent two 10 sessions (each during two weeks) of computer-assisted physical therapy focused on neuro-muscular movement and balance control. Results: Post-therapy evaluations showed significant improvements in both bipodal and unipedal static balance, segmental and overall body posture, and spinal musculoskeletal functionality. The therapy effectively addressed the postural asymmetries and shifted the center of gravity closer to the optimal vertical posture point. Conclusion: Computer-assisted physical therapy with visual feedback significantly improved posture, balance, and spinal functionality in patients with Lyme disease-related neuro-motor sequelae. This approach facilitated the restoration of muscle coordination and enhanced motor control, aligning with findings from the existing literature.

Keywords: Lyme Disease; Global Postural System; unipedal static balance; BACKFIX; global posture; spine; physical therapy

INTRODUCTION

The specialized literature lacks scientific studies on the functional evaluation and neuromusculoskeletal recovery in Lyme Disease (LD). Approximately 80 articles from the past decade are available in databases, primarily focusing on early detection and antibiotic treatment. No studies provide information on potential methods for functional evaluation or physical therapy-based recovery for musculoskeletal dysfunctions caused by inflammation secondary to Borrelia infection.

LD is caused by the bite of a tick infected with Borrelia. The disease progresses through three stages and can result in multisystem complications. When the nervous system is affected, it is referred to as neuroborreliosis, which may manifest as meningitis, mononeuritis multiplex, or cranial neuritis, including inflammation of the vestibulocochlear nerve [1]. Exclusive involvement of the vestibular system can lead to dizziness and balance instability [2]. Musculoskeletal symptoms can appear at any stage, including early localized infection, often resulting in patients being misclassified into the incorrect stage [3].

We describe motor control and the potential effects of systemic inflammation caused by borreliosis, followed by the stages of assessment and recovery, and the conclusions drawn from these steps.

Although the exact mechanism by which LD causes small fiber neuropathy is unknown, several potential mechanisms of neuronal damage are considered. These include the direct neurotoxic effect of the spirochete, neuroinflammation, and increased autoimmunity affecting the peripheral nervous system (PNS) with subsequent impacts on muscles, joints, and specific post-infection pains. However, a clear causal link between neurological symptoms and Borrelia infection cannot be

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established for patients with polyneuropathy/polyneuritis who test positive for Borrelia [4].

Among the genospecies of Borrelia burgdorferi sensu lato: Borrelia burgdorferi sensu stricto (s.s.), Borrelia garinii and Borrelia afzelii, Borrelia burgdorferi s.s. has the strongest potential to damage joints [5]. It is the most common cause of LD in the United States [3, 6], while infections with this pathogen are much less common in Europe [7-9]. The pathogenesis of LD is primarily driven by a strong inflammatory reaction [5], resulting in a perivascular collection of lymphocytes, macrophages, and scattered mast cells in the interstitial tissue, as typically observed in histopathological examinations of severe LD cases [9].

Previous studies have shown that late manifestations affecting the nervous system or joints can appear months or years after the initial infection, presenting symptoms such as fatigue, difficulty walking, posture disorders, and muscle pain. These symptoms are also present in the subject of our study, secondary to the diagnosis of borreliosis [10].

The examination and treatment of patients with motor control disorders are based on theories of motor control that guide the understanding of movement mechanisms [11-14]. In our study, we utilize systems theory as a foundation for clinical applications. Systems theory posits that movement arises from the interaction of various processes, including perceptual, cognitive, and motor processes, as well as the interactions between the individual, the activity, and the environment.

The severity of symptoms observed in all the patients with LD that we have evaluated has led us to pay more attention to this condition. As a result, our study focuses on evaluating and recovering a patient with LD using methods and applications informed by previous scientific studies. We analyzed a patient with sequelae following LD, including postural, walking, and static and dynamic balance disorders, muscle fatigue, changes in balancing synergies, walking base, and the projection of the General Center of Gravity (GCG). We conducted initial and final tests after a series of 10 and 20 sessions of specific physical therapy exercises.

Pioneers in the study of motor control and movement, such as Bernstein and Latash [15-17], along with Charles Sherrington (1857 - 1952), Thomas Graham Brown (1882-1965), and Walter Hess (1881-1973), have significantly contributed to our understanding of joint freedom, redundancy, and muscle-articular synergies. Charles Sherrington contributed to the understanding of inhibition, spinal-muscle connectivity, and the sensory-motor cortex. Thomas Graham Brown researched central movement programming and pattern generation mechanisms. Walter Hess studied the central coordination of the autonomic system and anticipatory motor behavior. Bernstein, recognized posthumously by Western colleagues, demonstrated a central hierarchy of postural control mechanisms and distributed, parallel processing of movement.

Bernstein also participated in developing theories of motor programs, recognizing that understanding neural control of movement requires knowledge of the system's characteristics in response to external and internal stimuli [16]. His distributed model of motor control showed that central commands could produce different motions due to external forces and initial conditions. His student, Mark Latash, furthered this work by demonstrating that synergies evolve to ensure flexible and stable performance in motor activities [17].

Postural control for stability and body orientation in space requires a complex interaction between the musculoskeletal and neural systems. This includes joint amplitudes, intersegmental biomechanical relationships, muscle physiology, spinal flexibility, neuromotor processing, synergies, perceptual and sensory processes, and their central integration.

Research has concluded that postural control is not managed by a single system but depends on various intrinsic and extrinsic factors [18]. Initial studies highlighted the importance of maintaining the center of mass (COM) within certain limits for static posture. However, subsequent studies demonstrated that stability limits are not fixed and vary with individual characteristics or actions undertaken. When recovering balance, individuals tend to restore COM disturbances rather than segmental alignment disturbances, suggesting that COM is a key variable controlled by the central nervous system during postural control.

Further studies have shown that analyzing the relationship between the center of gravity (COG) and the center of pressure (COP) provides a better picture of stability [19-24]. Their interaction has been considered and used to measure and estimate posture control effectiveness in our study.

As actions have both stability and orientation components, and certain actions prioritize orientation over stability, research by Shumway-Cook & McCollum [25] and Horak & Macpherson [26] has demonstrated that stability and orientation vary with each action. The body can behave like an inverted pendulum, employing various strategies (ankle, hip) for both static and dynamic balance [21].

Bernstein's assertion that "Movement coordination is the process of mastering the redundant degrees of freedom of a mechanism in motion" [16] encapsulates the essence of motor control theories used in our study.

Equilibrium

While bipedal standing is characterized by minor postural imbalances, dynamic balance involves the integration of sensory information from the visual, vestibular, and proprioceptive systems in conditions of postural instability.

There are several theories about how sensory organization adapts to a changing environment, with two primary ones being: the intermodal theory of sensory organization by Stoffregen and Riccio [27], which posits that all sensory systems equally and continuously contribute to postural orientation; and the sensory weighting model, which suggests that the central nervous system adjusts the importance of each sensory system based on their accuracy for orientation and postural stabilization.

Torres and Oviedo [28] examined the structure and organization of muscle synergies for balance control, highlighting that a muscle can contribute to multiple synergies, each with a unique role. They demonstrated that muscle synergies can be continuously modulated by feedback signals to create postural adjustments, indicating that the central nervous system uses both pre-programmed synergies and continuous feedback control to regain stability.

Nashner et al. [29] investigated the selection of sensory information by the CNS for postural control by designing a dynamic platform with a moving visual wall to study sensory interactions in maintaining posture and balance. This approach allowed for the measurement and recording of posture and balance under various conditions.

Several studies on normative values using static platforms have examined the performance of normal subjects under varying sensory information conditions [29-33]. These studies have shown that adults and children over seven years old (the age of vestibular maturation) maintain balance well under all conditions of sensory disturbance.

The inability to maintain a stable static posture has significant functional consequences in neurological pathologies. It necessitates using the arms and hands for balance, detracting from daily activities [34-38]. Moreover, postural instability and the inability to stand on one leg for more than six seconds increase the risk of falls threefold.

Springer's 2007 study [39] showed that balance disorders are prevalent in patients with specific diseases or traumas, particularly head injuries, peripheral neuropathies, or acquired neurological conditions. Neurological pathologies can disrupt one of the postural control strategies (e.g., loss of pre-programmed synergies) while leaving the other (continuous feedback control) intact, necessitating complementary studies to distinguish between these aspects and propose specific solutions.

For the main types of static/dynamic balance (postural control/anticipatory and reactive postural control), numerous clinical tests measure performance, including the unipedal stance and computerized posturography. Our study used such tests to assess the patient's condition at the beginning and end of the recovery program.

Unipedal standing is a highly challenging situation for humans and allows researchers and clinicians to assess the effects of aging, disease, trauma, and the influence of multiple sensory systems. The single-leg stand test, which requires minimal equipment, measures balance aspects and shows abnormal values in conditions such as peripheral neuropathies and intermittent claudication. [35,36]

Various studies demonstrated the importance of maintaining unipedal posture and balance by examining corticomuscular coherence between the ankle joint and the sensorimotor cortex. This study showed that the sensorimotor cortex is directly involved in postural control during unipedal standing, compensating for high postural demands due to the low support base. Normative values in the literature indicate a significant decrease in unipedal stance time with age and pathology [40, 41].

Alain Berthoz et al. [20] demonstrated that during complex movements, the head is intermittently stabilized under gaze and fixation control, allowing it to act as an inertial guidance platform for controlling multisegmental movements. The otolithic organs, the saccule, and utricle, detect the linear accelerations of the head and provide a gravitational reference used not only to correct posture but also for perceptual actions requiring spatial orientation, including mental map rotation based on sensory information from all senses.

Merton's Servo-Control Hypothesis

The interaction between motor and sensory processes is bidirectional, and the importance of sensory information for motor control was established many years ago. The traditional feedforward and feedback control mechanisms could not fully explain the coactivation of the alpha-gamma muscle loops, necessitating alternative theories such as the equilibrium point hypothesis and the hierarchy of synergies to explain how correct posture is maintained during external destabilizations [42].

Merton proposed a model that adjusts the equilibrium point, where the CNS controls both speed and position during rapid segmental movements. Degenerative, infectious, and metabolic diseases have disrupted the transmission of sensory information from the periphery to the CNS, affecting the parameters and components of posture and movement control. Disorders of nerve conduction from proprioceptors to the brain, as seen in neurological or diabetic patients, result in significant balance issues, making it difficult for patients to stand upright with their eyes closed on a static plane [42].

Posture, a term introduced by André Bregegère in 1955 [43], is defined as a momentary attitude or body position [44]. It involves the synergistic and coordinated action of the musculoskeletal system and the central and peripheral nervous systems to maintain body stability, balance, and constant relations between body segments and the environment [45-47]. Correct posture involves the alignment of all joints, and any misalignment can lead to muscle-joint imbalances [48].

Maintaining postural stability requires the co-participation and complementarity of actions from all support components, followed by motor actions (balancing, distribution of motor control tasks), which can be synchronous or asynchronous, simultaneous, or alternating depending on the demands [44,49]. Optimal body alignment in an upright position involves:

Head: Maintained by neck muscles. Insufficiency or habitual forward tilt increases muscle demand.

Trunk: Tends to fall forward due to its weight and the head's weight, counteracted by vertebral muscles.

Shoulders: The scapular belt and upper limbs' weight cause the shoulders to fall and scapulae to separate from the spine, counteracted by shoulder girdle muscles.

Pelvis: Key to maintaining correct posture. Anteversion is balanced by gluteal and posterior thigh muscles, whose hypotonia causes anterior trunk tilt. Retroversion is balanced by rectus abdominis, obliques, and iliopsoas muscles, whose hypotonia causes posterior tilt.

Lower limbs: Stability is ensured by plantar flexor muscles and triceps surae, especially the soleus [45].

Postural defects can lead to fatigue, muscle strain, and pain in later stages, potentially affecting vital organs, particularly in the abdominal region. Our study integrates current scientific conclusions and hypotheses to address parameters affecting motor control and static and dynamic postural control in our subject, considering the literature review.

Motor control theories are inherently unfinished, always allowing room for new information from recent studies on normal and pathological brain and PNS functioning. Neuroscientists identify the scientific basis for movement disorders, while clinicians develop applications of this research, as theories are considered more or less useful based on their problem-solving efficacy for patients with movement disorders.

In this context, we present a study where a patient with Lyme disease sequelae is compared to literature findings regarding posture, balance, and neuromuscular control of movement. Previous works by Schor D, Schor V et al.[50-52] introduced the BACKFIX Method, used for spine functional impairments in preventive care. This study evaluates its application to a complex disease like LD, characterized by neurological symptoms affecting balance, walking patterns, general movement control, and muscle strength imbalance.

We demonstrate the patient's condition evolution using physical therapy with visual feedback on the rectangular force-amplitude model. Improvements in agonist-antagonist cooperation lead to enhanced muscle strength, functional muscle-joint balance of the spine, posture, and walking pattern. The patient exhibited muscle cramps in the calf and foot, pronounced thigh flexor fatigue during walking, insecurity in unipedal support, jerky walking with a wide support base, and reduced standing time in unipedal support.

MATERIALS AND METHODS

We performed the following measurements:
• Computerized somatoscopic examination
• Forces, amplitudes, and mechanical work on the supporting muscles of the trunk, enabling a computerized muscle-articular evaluation of the trunk
• Bipodal static balance - stabilometry
• Unipedal static balance

We utilized the GPS System (Global Postural System) for computerized somatoscopy and computerized static bipodal balance tests, provided by UNEFS Bucharest (University of Physical Education and Sport from Bucharest), and the Ergocontrol System for musculo-articular functionality tests of the spine using the Backfix Method, technology provided by Medisport Company.

An initial evaluation and two intermediate evaluations were conducted. For the static one-legged balance test, we measured the hold time while standing on one leg. An initial evaluation and two intermediate evaluations were conducted. For the static one-legged balance test, we measured the hold time while standing on one leg

RESULTS

Initial Assessment Results

Computerized Somatoscopy Test

Front:
• Right shoulder slightly lowered and rotated anteriorly
• Left shoulder slightly raised
• Right hip slightly lowered
• Left hip slightly raised

Profile:
• Abdominal hypotonia with increased lumbar curvature
• Projection of the GCG (general center of gravity) 11 cm anterior to the normal position

Back:
• Left shoulder blade normally positioned
• Right shoulder slightly lowered and rotated anteriorly
• Left shoulder slightly raised
• Right hip slightly lowered
• Left hip slightly raised

Evaluation of the Muscle-Articular Functionality of the Spine

The results of the computerized musculo-articular measurements regarding the muscular support of the spine are presented in Table 1. The movements were performed with difficulty and were jerky, which is characteristic of the neurological sequelae of the condition.

Table 1: Initial muscle-articular evaluation (3.02.2023)

Test segment	F(daN)	L(cm)	Lm(J)
Direct – abdominal Indirect – lumbar	5.5	26	14.47
Direct- Scapular girdle ½ anterior, thorax anterior Indirect – anterior and posterior muscle groups of the trunk	9.31	49	45.45
Direct- Scapular girdle posterior ½ of the trunk Indirect – anterior and posterior muscle groups of the trunk	8.47	39	32.85

Resources and methods used in recovery

The recovery protocol involved 20 sessions of exercises utilizing visual feedback on force-amplitude curves, performed on the Ergocontrol System. This protocol aimed to restore agonist-antagonist cooperation within muscle groups and chains responsible for global body posture while also focusing on strength enhancement through movement control exercises targeting deficient muscle groups and chains.

Each session included walking exercises designed to integrate the improvements from the neuro-muscular movement control exercises, to enhance the walking pattern.

Results After 20 Recovery Sessions

There was a noticeable improvement in overall body posture and a tendency towards optimizing the indices of musculo-articular functionality of the spine. The results from the intermediate evaluations demonstrate progressive improvements in all measured parameters, as detailed in Tables 2 and 3.

Table 2: Intermediate muscle-articular evaluation (27.02.2023)

Test segment	F(daN)	L(cm)	Lm(J)
Direct – abdominal Indirect – lumbar	15.6	41	64.93
Direct- Scapular girdle ½ anterior, thorax anterior Indirect – anterior and posterior muscle groups of the trunk	181	61	110.29
Direct- Scapular girdle posterior ½ of the trunk Indirect – anterior and posterior muscle groups of the trunk	179	58	104.37

Table 3: Intermediate muscle-articular evaluation (26.03.2023)

Test segment	F(daN)	L(cm)	Lm(J)
Direct – abdominal Indirect – lumbar	20.8	49	103.5
Direct- Scapular girdle ½ anterior, thorax anterior Indirect – anterior and posterior muscle groups of the trunk	21.5	66	140.7
Direct- Scapular girdle posterior ½ of the trunk Indirect – anterior and posterior muscle groups of the trunk	213	56	118.2

The evolution of the somatic functionality of the trunk

Spine Pathology and Accident Risk Scale:
- < 0.50 = High Risk
- 0.50-0.75 = Medium Risk
- 0.75-0.95 = Low Risk

Initial Personal Levels:
- Lumbar: High
- Antero-posterior Thoracic: Medium

After Two Series of 10 Physical Therapy Sessions:
- Lumbar: Medium
- Antero-posterior Thoracic: Low

Chart number 1 illustrates the progress in muscle-articular functionality indices of the spine, specifically Thoracic Antero-posterior and Thoraco-lumbar, as assessed by Test 2 and Test 3. These improvements are also evident in the overall body posture, with notable

enhancements in the static balance and the projection of the GCG (see Figure 1).

Table 4: Segmental and intersegmental muscle-articular functionality ratios of the spine

Segmental and inter-segmental ratio	Optimal values	Personal values 03.02.2023	Personal values 27.02.2023	Personal values 26.03.2023
Thoracic anterior - posterior	0.85 - 0.95	0.73	0.94	0.84
Thoraco-lumbar	0.85 – 0.95	0.31	0.59	0.73

Chart number 1: Indices of muscle-articular functionality of the spine - Thoracic antero-posterior and Thoraco-lumbar

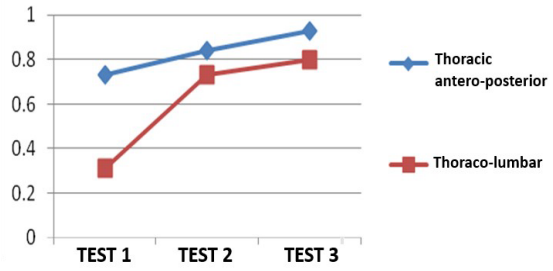


Figure 1: The improvements of the static ballance and the projection of the General Center of Gravity (CGG)

Overall analysis
Average distance from ideal barycentre X (mm) -99
Average distance from ideal barycentre Y (mm) 230
Length of curve; (mm) 17,013
Confidence ellipse area (mm²) 224,306
Curve / area ratio 0.076
Maximum speed (mm / s) 13,664
Right / Left fundamental frequency (Hz) 0.05
Overall analysis
Average distance from ideal barycentre X (mm) 6
Average distance from ideal barycentre Y (mm) -29
Length of curve; (mm) 279
Confidence ellipse area (mm²) 134
Curve / area ratio 2.1
Maximum speed (mm / s) 47

Unipedal Balance:
•Initially, unipedal support was impossible.
•After ten sessions, balance time increased to 21 seconds.
•After 20 sessions, the balance time reached 30 seconds.

General Center of Gravity (GCG)

Projection: Figures 2, 3, 4, and 5 depict the improvement in the migration of the General Center of Gravity in four positions: standing with eyes open, standing with eyes closed, facing left, and facing right.

Figure 2: The improvement of the migration of GCG in the position of stand-up face to the right side

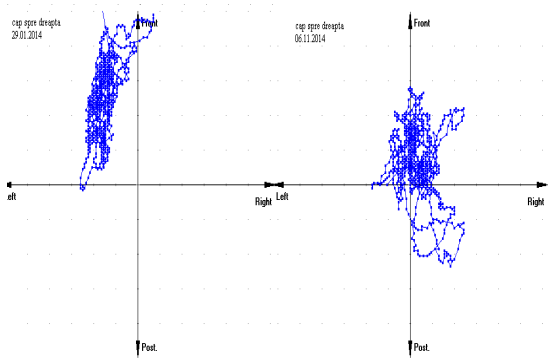


Figure 3: The improvement of the migration of GCG in the position of stand-up face to the left side

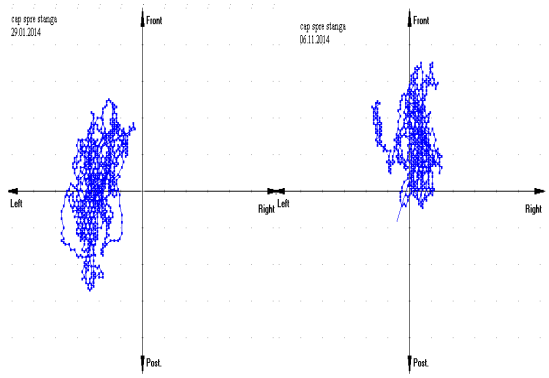


Figure 4: The improvement of the migration of GCG in the position of stand-up eyes closed

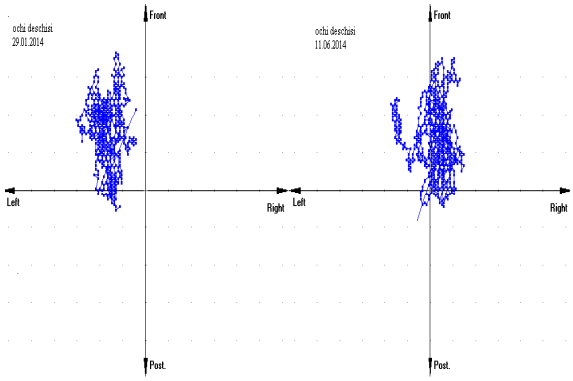
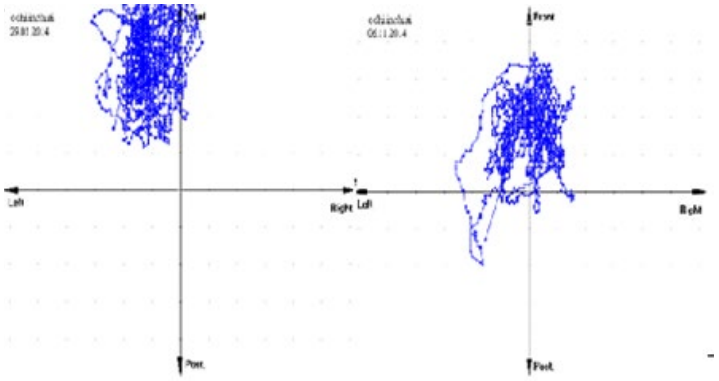


Figure 5: The migration of GCG improved in the position of standing up and eyes open



DISCUSSION

The key outcomes and benefits observed after completing two series of 10 physical therapy sessions in the study are presented in the following.

After Two Series of 10 Physical Therapy Sessions:

- Increased muscle strength and joint amplitude at the shoulder girdle.
- Continued need for abdominal muscle strength improvement to balance spinal muscle support.
- Enhanced muscle-articular functionality indices for the Thoracic Antero-Posterior and Thoraco-Lumbar regions, showing improvement from 0.73 to 0.84 and from 0.31 to 0.73, respectively.
- Balance time in the unipedal position with eyes open increased from 0 to 30 seconds.
- Improved gait from a jerky, insecure pattern to a smooth, balanced walk.
- During computerized somatoscopic evaluation, overall body posture improved, with the anterior projection of the CGG reducing from 11 cm to 5 cm from the normal projection.

The BACKFIX Method:

- Led to improved posture by optimizing muscle-articular functionality indices of the spine.

Visual Feedback on Force-Amplitude Patterns:
• Restored agonist-antagonist cooperation, positively affecting gait and balance motor control.

Optimized Functional Musculo-Articular Balance:
• Resulted in visible improvements in posture and walking pattern.

Risk Reduction:
• The risk of spinal pathology and accidents improved, moving from medium to low risk, with enhanced muscle chain synergies supporting proprioceptive and sensory system integration in unipedal stance.

The observed benefits from targeted physical exercises confirm previous studies on the uniqueness of bipodal and unipedal stance control, inter-segmental coordination, and the antigravity function of the leg extensors. Most cases of LD resolve after one course of therapy, although some patients experience gradual symptom relief even after treatment ends; therefore, follow-up assessments are recommended 3 months post-therapy. In some cases, symptoms persist despite antibiotic treatment, leading to the term "antibiotic-refractory LD", defined as persistent synovitis lasting more than 1 month after two four-week oral antibiotic courses or more than 2 months after intravenous ceftriaxone treatment [53].

Untreated arthritis may eventually resolve on its own, but it can persist for years, with some cases of LD lasting 7-8 years [54,55]. Potential treatments for patients with post-arthritis LD include non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), biologic agents, intra-articular steroids, and arthroscopic synovectomy [55,56].

The strengths of this study lie in its focus on the functional evaluation and rehabilitation of patients with Lyme disease-related neuro-muscular issues, an area with limited prior research. The use of computer-assisted physical therapy, employing technologies like the GPS Posture-test System and BACKFIX Technology, allowed for a precise and objective assessment of balance and posture, leading to significant improvements in the patients. These technologies facilitated a more thorough understanding of musculoskeletal impairments and offered targeted interventions that improved both static and dynamic balance, posture, and muscle coordination.

However, some limitations must be noted. The rehabilitation was conducted on one patient, and this limits the generalizability of the results. Additionally, the long-term sustainability of the therapy outcomes remains uncertain, and further follow-up studies are needed to verify the persistence of improvements beyond the immediate post-treatment period. Another limitation is the lack of control, which would have strengthened the validation of the study's findings.

Future research in this domain should focus on expanding the sample size and incorporating control groups for comparative analysis. Long-term studies are also crucial for understanding the chronic impact of rehabilitation techniques. Finally, integrating more advanced technologies, such as virtual reality or machine learning algorithms for personalized therapy adjustments, could further enhance patient outcomes in neuro-muscular recovery for Lyme disease.

CONCLUSION

This study demonstrates the effectiveness of computer-assisted physical therapy using technologies such as the GPS Posture-test System and BACKFIX Method in addressing the neuro-muscular and postural impairments associated with Lyme disease sequelae. Patients exhibited significant improvements in static and dynamic balance, posture, and musculo-articular functionality after completing two series of physical therapy sessions. The visual feedback provided during therapy sessions played a crucial role in restoring agonist-antagonist cooperation and enhancing motor control.

In conclusion, targeted physical therapy combined with advanced postural assessment technologies offers an effective means of improving functional recovery in Lyme disease sequelae patients, supporting their overall motor control and quality of life.

Conflicts of interest and sources of funding

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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Authors' contribution

Conceptualization D.S. and V.S.; methodology D.S.; software V.S.; validation D. S., L.G.E. and A.G.; formal analysis R.P.; investigation P.S.F.; resources S.S. and M.B; data curation R.R.G.; writing—original draft preparation D.S.; writing—review and editing L.G.E and A.G.; visualization R.R.G.; supervision L.G.E.; project administration D.S.; funding acquisition V.S. All authors have read and agreed to the published version of the manuscript elaboration.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of MEDISPORT Physical Therapy Clinic (11/30.03.2023).

Patient consent for publication

Informed consent was obtained from all subjects involved in the study.

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ARTICLE

Navigating Cancer: Mental Adjustment as Predictor of Somatic Symptoms in Romanian Patients- A Cross-Sectional Study

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Abstract: Objective: This study aimed to examine the relationship between mental adjustment mechanisms and somatic symptoms in cancer survivors, a topic with limited research in Psycho-oncology. Methods: In this exploratory cross-sectional study, 88 cancer patients were surveyed using the Somatic Symptoms Scale (SSS-8), the Somatic Symptom Disorder Scale (SSD-12), and the Mini-Mental Adjustment to Cancer Scale (MINI-MAC). Additional questions were asked regarding cancer stage, treatment, and illness relapses. Data collection occurred over one month at a local oncology unit. Results: Several significant correlations were observed between the scales and subscales of the instruments applied during this study. The most important results showed that maladaptive adjustment mechanisms were significantly associated with somatic symptoms, while adaptive mechanisms were not. However, "fighting spirit," an adaptive mechanism, acted as a moderator between somatic symptoms and their psychological impact (effect size $t = 0.157$, $p < 0.05$). Lower "fighting spirit" scores correlated with higher SSS-8 and SSD-12 scores, indicating its potential protective role. Conclusion: A more specific assessment of somatic symptoms and their link to mental adaptation to cancer is needed. Psycho-oncological interventions should address both adaptive and maladaptive adjustment mechanisms due to their significant influence on patient outcomes.

Keywords: cancer, mental adjustment, somatic symptoms, adaptive mechanisms, maladaptive mechanisms, Psycho-oncology

INTRODUCTION

The prevalence of cancer is increasing worldwide, with almost 18.1 million cases in 2020 and a rise of 28 million cases in 2040 [1]. Romania has a lower incidence of cancer related to EU mean value, but the mortality of this disease is higher, which reflects the overall weakness in the cancer approach in our country, Romania having among the highest oncological mortality rates in Europe [2,3]. Approximately 100,000 people are diagnosed with cancer in Romania every year, a number that could be even higher. In response, Romania approved a National Plan for Beating Cancer in 2022 to be implemented during 2023-2026. Addressing the cancer burden will require sustained efforts to improve cancer prevention, early diagnosis, treatment access, and cancer surveillance systems [4,5,6]. Key measures included in the country`s National Plan for Beating Cancer are integrated and present a multidisciplinary approach, health innovation fund, cancer registry, and data collection, clinical guidelines and protocols, and oncological experts' boards. Among these last ones, a special place will be highlighted by the Psycho-oncological approach. Psycho-oncology is facing significant challenges, including major gaps in services and a critical shortage of specialized professionals, resulting in a nationwide deficit in Psycho-oncology care. However, the concepts of mental adjustment, psychological distress, and quality of life are very scarcely mentioned in local literature. Broader searches for Eastern Europe yielded limited similar results, indicating a general lack of research [7].

Patients with cancer may present more frequent anxiety, depressive symptoms, somatic symptoms, and overall psychological imbalance due to the perceived poor outcome and recurrence of the disease. Recent research has reinforced the link between psychological distress and an increased likelihood of mortality and worse survival outcomes [8]. Psychological distress in patients with cancer is defined as the psychological damage that impairs an individual's ability to operate. This illness comprises a range of emotional and behavioral features arising from the diagnosis and prognosis uncertainty [9]. Prior studies have emphasized the importance of depressive disorders and extreme emotional response patterns as crucial elements in diminishing the quality of life of these patients. It is important to acknowledge the

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interconnection between anxiety, sadness, and somatic symptoms in the context of cancer experience [10].

The cancer adjustment frame was developed by Watson and includes five adjustment mechanisms: fighting spirit, avoidance–denial, fatalism–stoic acceptance, helplessness–hopelessness, and anxiety [11]. Mental adjustment to cancer refers to the process of coping with emotional distress and restoring mental balance after a cancer diagnosis. It involves specific attitudes and strategies that patients use to adapt to the challenges of cancer and its treatment. Patients with a fighting spirit tend to have better quality of life and lower anxiety/depression compared to those with a helpless/hopeless attitude [12,13]. Maladaptive coping styles like helplessness/hopelessness are associated with a higher risk of mortality in some studies, although the evidence is not yet conclusive [12]. Factors like age, performance status, social support, and satisfaction with support can influence mental adjustment. Mental adjustment, economic status, perceived disease severity, and symptom severity directly affect the comprehensive quality of life outcome (CoQoLO) in terminally ill patients [12,13].

Somatic symptoms constitute about 50% of all general medical consultations, remaining prone to further investigations and bringing frustration to both patients and doctors in approximately one-third to one-half of cases. Both physiological and psychological variables seem to contribute to the reporting of somatic symptoms, especially in individuals with long-term medical conditions [14]. These symptoms are linked to significant limitations in functioning, disability, and utilization of healthcare services, even when considering other medical and mental conditions [14,15,16]. Research on the frequency of somatic symptoms in cancer has frequently concentrated on individuals with advanced stages of the disease or specific forms of cancer observed at specialized medical facilities [12,13,17,18]. Research revealed that a minimum of 30% of patients with cancer experience the following symptoms: fatigue and low energy, unspecified pain, loss of appetite, constipation, sleep disorders, and dizziness. The connection between psychological distress and reporting of somatic symptoms, also known as somatization, has only been examined in a limited number of small-scale research on cancer [15, 16,19,20]. This gap is significant since several studies in non-cancer medical populations have shown a high occurrence of somatic symptoms, even among symptoms that are regarded to be more specific to a particular disease. Moreover, the somatization concept refers to the expression of psychological distress through physical symptoms. Somatic symptoms, the term we chose to use throughout this paper, conversely denotes the way emotional stress can materialize as physical symptoms. A thorough comprehension of this matter is crucial to effectively address the psychological requirements of individuals with cancer, thereby enhancing their quality of life and their capacity to manage the illness [13,16,21]. Despite the recognized importance of mental adjustment on QoL and prognosis in cancer care [12], there is limited research focusing on the interplay between mental adjustment and somatic symptoms specifically.

This study aims to fill this gap by exploring the relationship between mental adjustment to cancer and somatic symptoms in patients with cancer. The findings could provide valuable insights for Psycho-oncology professionals enhancing supportive care strategies, ultimately improving patient outcomes and quality of life. The primary objectives of this study are to assess the levels of mental adjustment to cancer among Romanian patients, to measure the prevalence and severity of somatic symptoms, and to investigate their relationship with mental adjustment as being predicted by certain types of adaptive and maladaptive mechanisms. We hypothesize that maladaptive coping styles will predict somatic symptoms and their burden, while adaptive coping styles may represent protective factors in the onset and maintenance of somatic symptoms. This cross-sectional study involved a sample of Romanian patients, implementing validated psychological assessment tools to evaluate mental adjustment and somatic symptoms. Statistical analyses were conducted to explore correlations and identify significant predictors.

MATERIALS AND METHODS

Study design

This study employed a cross-sectional design to investigate the relationship between mental adjustment to cancer and somatic symptoms and their burden in Romanian cancer survivor outpatients.

Participants

A total of 88 patients with cancer were recruited from the cancer department of Elias University and Emergency Hospital in Bucharest, Romania, for one month, between May and June 2023. Inclusion criteria were: a confirmed diagnosis of cancer in the last three years, age 18 years or older, out-patients regularly monitored during their cancer treatment follow-up, and ability to understand and provide informed consent. Exclusion criteria included: severe cognitive impairment, DSM-5-TR diagnosis of a severe psychiatric disorder such as schizophrenia, depression or bipolar disorder currently or in the past based on information obtained from behavioral scales, a clinical psychiatric evaluation, and the Structured Clinical Interview for DSM Disorders [22]; diagnosis of neurological conditions (e.g., Parkinson's disease, multiple sclerosis) that could affect cognitive or emotional processing, other genetic diseases or syndromes that might affect mental adjustment mechanisms or cognitive function.

Ethical approval

The study was approved by the Ethics Committee of the Elias University and Emergency Hospital of Bucharest, Romania (nr. 9286/2023). All participants provided written informed consent before participation.

Data Collection

Data were collected through structured interviews and self-administered questionnaires. The following tools were used:

Socio-demographic data- this section included information such as age, gender, education level, employment status, marital status, residence, income level, number of children, cancer stage, cancer location, chemotherapy, hormonal, surgery, and radiotherapy history.

Mini-Mental Adjustment to Cancer (Mini-MAC) – The questionnaire, designed by Watson[11], used the Romanian-translated version [23]. The mini-MAC questionnaire consists of 29 items, assessing different ways of coping with cancer: Anxiety- refers to fear concerning the disease without prior control which is anxiety-causing; Fighting spirit- refers to framing cancer as a challenge that may prone the patient to take action and fight it; Helplessness–hopelessness- refers to feelings of passivity and fatalism towards cancer leading to submission; Positive revaluation- refers to framing the life already lived in the light of satisfaction. Coping with cancer can be made within a constructive framing including fighting spirit and positive revaluation while anxiety and helplessness may represent a destructive pattern of coping. The items are rated on a scale of 1 to 4 representing variations of responses from „definitely not" to „definitely yes" which may offer results for each of the coping strategies from 7 to 28 points. The higher the score the more frequent and intense each mental adjustment mechanism is represented.

Somatic Symptoms Scale-8 (SSS-8)- The 8-item was developed after a version of the Patient Health Questionnaire-15 (PHQ-15) [24] and validated in the general population and Romanian population [25] as well as inpatient and outpatient settings, with SSS-8 not yet validated in Romanian language [26] to detect somatic symptoms burden. The level of the experienced somatic symptoms is scored from 0 meaning „not at all" until 4 which represents „very strongly". The results are grouped into different categories with minimum, low, medium, and high groups containing symptoms such as pain in the arms, legs, or joints, gastric problems, insomnia, unspecified thoracal pain or trouble breathing, fatigue, or different ranges of headaches.

Somatic Symptom Disorder-12 (SSD-12)- this tool was first developed by Toussaint et al. [27] and focused on criterion B of the Somatic Symptom Disorder (SSD) diagnosis including subscales on cognition, affect, and behavior. 12 items are scored from 0 meaning „never" to 4 meaning „very often". The scale was already validated in outpatient settings [28], and the Romanian version used, was previously translated and validated [19,29]. 18 score was chosen to screen for potential cases by the creators of the scale with studies still being concerned with the validity of cut-off points [30].

Procedures

Participants were approached during their routine medical visits and invited to participate in the study. Those who consented were given the questionnaires to complete on-site, with instructions for returning them. Structured interviews were conducted on-site by trained researchers and clinical psychologists to ensure consistency and accuracy in data collection and that the data collection processes did not interfere with the regular cancer follow-up procedure.

Statistical Analysis

Data were analyzed using JASP software [31]. In line with the explorative nature of our study, we first described the demographics of the study participants. The internal consistency of psychometric scales was assessed using Cronbach's alpha coefficient, and all instruments had coefficients above 0.7, which is the minimum acceptable value for proper reliability. Descriptive statistics (means, standard deviations, frequencies) were used to summarize the demographic and clinical characteristics of the sample. Pearson correlation coefficients were calculated to examine the relationship between mental adjustment and somatization scores. Multiple regression analyses were conducted to identify significant predictors of somatic symptoms, controlling for potential confounders and considering standard $p\text{-value} < 0.05$

RESULTS

Psychometric scales reliability

All the psychometric tools used proved to be reliable. As confirmed in our analysis, a tool needs to have a Cronbach Alpha of at least 0.7 to be used. Moreover, SSS-8 presented values of 0.815, SSD-12 of 0.910, and Mini-MAC of 0.879, with all subscales also confirmed to be reliable.

Descriptive analysis

Socio-demographic data

Table 1 presents the socio-demographic characteristics of the participants. The most frequent age interval of the participants was 41-50 years with over 70% being in the age interval of 41-60 years. The sample included 86 females (97.7%). 69,3% were married, over 68% graduated from at least one university, and 75% declared a good financial status. Concerning cancer, 82,5% had local cancer, and 71% presented breast cancer with various periods since surgery, from less than one year (20,4%) to over three years (36.6%). 79% declared chemotherapy intervention, while 64% declared radiotherapy, with over 90% presenting surgery history.

Psychometric scales scores

The scores for SSS-8 indicated moderate somatic symptoms burden (mean= 10.214, SD=5.903), while SSD-12 presented a mean of 16.753, close to the cut-off point of 18, considered for SSD screening [30]. Also, the behavioral aspect of SSD-12 presented a mean of

6.110 (SD=3.256). Concerning Mini-MAC subscales, we identified anxious preoccupation (mean=17.352; SD=4.857) and helplessness (mean=14.082; SD=4.198) among the highest-scoring mechanisms checked.

Table 1: Socio-demographic characteristics

Variable	Category	Frequency	Percent	Valid Percent	Cumulative Percent
Age	20-30	3	3.409	3.409	3.409
	31-40	6	6.818	6.818	10.227
	41-50	36	40.909	40.909	51.136
	51-60	27	30.682	30.682	81.818
	>60	16	18.182	18.182	100.000
Gender	Feminine	86	97.727	97.727	97.727
	Masculine	2	2.273	2.273	100.000
Marital Status	Married	61	69.318	69.318	69.318
	Single	5	5.682	5.682	75.000
	Divorced	17	19.318	19.318	94.318
	Widowed	5	5.682	5.682	100.000
Education	Elementary	1	1.136	1.136	1.136
	Medium	25	28.409	28.409	29.545
	University	33	37.500	37.500	67.045
	Master, PhD	29	32.955	32.955	100.000
Financial Situation	Bad	16	18.182	18.182	18.182
	Good	66	75.000	75.000	93.182
	Very good	6	6.818	6.818	100.000
Cancer Stage	Local	73	82.955	83.908	83.908
	Advanced	14	15.909	16.092	100.000
Cancer Location	Breast	71	80.682	80.682	80.682
	Digestive	1	1.136	1.136	81.818
	Genital	15	17.045	17.045	98.864
	Respiratory	1	1.136	1.136	100.000
Time Since Surgery	<1 year	18	20.455	22.785	22.785
	< 2 years	14	15.909	17.722	40.506
	2-3 years	15	17.045	18.987	59.494
	>3 years	32	36.364	40.506	100.000
Chemotherapy	No	16	18.182	18.605	18.605
	Yes	70	79.545	81.395	100.000
Radiotherapy	No	30	34.091	34.483	34.483
	Yes	57	64.773	65.517	100.000
Hormone Therapy	No	35	39.773	39.773	39.773
	Yes	53	60.227	60.227	100.000
Surgical History	No	8	9.091	9.091	9.091
	Yes	80	90.909	90.909	100.000

Table 2: Psychometric scales scores characteristics

Variable	Valid	Missing	Mean	Std. Deviation	Minimum	Maximum
SSS-8	84	4	10.214	5.903	1.000	32.000
SSD-12	73	15	16.753	8.052	1.000	39.000
SSD--12_Cognitive	88	0	4.170	2.649	0.000	14.000
SSD12_Afective	88	0	5.784	3.758	0.000	16.000
SSD-12_Behavioral	73	15	6.110	3.256	1.000	15.000
MAC-Helplessness	85	3	14.082	4.198	8.000	28.000
MAC-Anxious preoccupation	85	3	17.353	4.857	8.000	29.000
MAC-Fighting Spirit	85	3	12.388	2.111	5.000	16.000
MAC-Cognitive avoidance	85	3	11.153	2.432	4.000	16.000
MAC-Fatalism	85	3	14.847	2.780	7.000	20.000

The missing data pertains specifically to the behavioral aspects subscale of the SSD-12, with approximately 17% of participants not completing this part of the scale. This indicates that the missing data is not spread across the entire SSD-12 scale but is confined to a particular subset. To address this, analyses related to the behavioral component were conducted on available data. This approach

minimizes data loss but may introduce bias if the missing data is systematic (e.g., patients with more severe symptoms avoiding completion). No imputation was used for the missing data, and as such, the findings should be interpreted with caution. Sensitivity analyses showed that the inclusion or exclusion of these cases did not substantially alter the overall findings of the study.

Correlation between all psychometric scales analysis

We found significant correlations between SSS-8 scores and overall SSD-12 score including affective and behavioral aspects subscales (r=0,63; r=0,57; p<.001), anxious preoccupation (r=0.328; p<.01), helplessness (r=0.354, p<.01) and significant negative correlations with fighting spirit (r=-0.299; p<.001). SSD-12 scores were significantly correlated with helplessness and anxious preoccupation (r=0.558, p<.001; r=0.578, p<.001) as seen in Table 3.

Table 3: Pearson correlation coefficients between different variables

Variable	SSS8	SSD12	SSD12_ Cog	SSD12_ Affect	SSD12_ Beh	Help-lessness	Anxious preoccupations	Fighting spirit	Cognitive avoidance	Fatalism
SSS8	—									
Pearson's r	—	0.537***	0.420***	0.630***	0.570***	0.354**	0.328**	-0.299**	-0.023	-0.171
p-value	—	1.615×10^-6	7.014×10^-5	1.318×10^-10	2.592×10^-7	0.001	0.003	0.007	0.837	0.126
SSD12	0.537***	—	0.796***	0.950***	0.919***	0.558***	0.578***	-0.195	0.257*	-0.004
p-value	1.615×10^-6	—	3.648×10^-17	1.515×10^-37	1.814×10^-30	3.581×10^-7	1.084×10^-7	0.101	0.030	0.971
SSD12_ Cog	0.420***	0.796***	—	0.695***	0.562***	0.407***	0.469***	-0.111	0.104	0.110
p-value	7.014×10^-5	3.648×10^-17	—	5.610×10^-14	2.360×10^-7	1.124×10^-4	5.838×10^-6	0.312	0.344	0.315
SSD12_Afectv	0.630***	0.950***	0.695***	—	0.844***	0.520***	0.614***	-0.199	0.198	-0.029
p-value	1.318×10^-10	1.515×10^-37	5.610×10^-14	—	6.586×10^-21	3.423×10^-7	4.054×10^-10	0.068	0.069	0.790
SSD12_Beh	0.570***	0.919***	0.562***	0.844***	—	0.565***	0.544***	-0.165	0.241*	-0.013
p-value	2.592×10^-7	1.814×10^-30	2.360×10^-7	6.586×10^-21	—	2.278×10^-7	7.828×10^-7	0.167	0.043	0.914
Helplessness	0.354**	0.558***	0.407***	0.520***	0.565***	—	0.693***	-0.414***	0.057	-0.275*
p-value	0.001	3.581×10^-7	1.124×10^-4	3.423×10^-7	2.278×10^-7	—	2.733×10^-13	9.071×10^-5	0.606	0.012
Anxious preoccupations	0.328**	0.578***	0.469***	0.614***	0.544***	0.693***	—	-0.239*	0.152	-0.132
p-value	0.003	1.084×10^-7	5.838×10^-6	4.054×10^-10	7.828×10^-7	2.733×10^-13	—	0.028	0.170	0.233
Fighting spirit	-0.299**	-0.195	-0.111	-0.199	-0.165	-0.414***	-0.239*	—	0.311**	0.734***
p-value	0.007	0.101	0.312	0.068	0.167	9.071×10^-5	0.028	—	0.004	2.878×10^-15
Cognitive avoidance	-0.023	0.257*	0.104	0.198	0.241*	0.057	0.152	0.311**	—	0.425***
p-value	0.837	0.030	0.344	0.069	0.043	0.606	0.170	0.004	—	6.071×10^-5
Fatalism	-0.171	-0.004	0.110	-0.029	-0.013	-0.275*	-0.132	0.734***	0.425***	—
p-value	0.126	0.971	0.315	0.790	0.914	0.012	0.233	2.878×10^-15	6.071×10^-5	—

**p < 0.05, **p < 0.01, ***p < 0.001*

Tables 3 and 4 show the contribution and significance of each predictor of MAC mechanisms to somatization as follows. Helplessness and anxious avoidance negatively predict somatization (t=2.520, p<.01; t=2.462, p<.01) while fighting spirit is moderator of the relationship between somatization (SSS-8) and its burden (SSD-12) (t= 0.157, p<.01) with low and medium values having a positive correlation which disappears at highest levels.

Table 4: Multiple regression analysis

Model	Unstandardized Coefficient (B)	Standard Error	Standardized Coefficient (Beta)	t	p-value
H_0 (Intercept)	17.060	1.002	—	17.026	0.013
H_1 (Intercept)	-22.708	9.161	—	-2.479	0.016
Helplessness	0.744	0.295	0.385	2.520	0.014
Anxious preoccupations	0.583	0.237	0.342	2.462	0.017
Cognitive avoidance	0.701	0.377	0.191	1.858	0.068
Fatalism	0.601	0.479	0.174	1.254	0.215
Fighting spirit	0.108	0.685	0.025	0.157	0.876

DISCUSSION

Our study showed that mental adjustment to cancer and somatic symptoms are significantly interrelated in patients with cancer. Specifically, only negative mechanisms such as anxious preoccupation and helplessness predicted somatic symptoms burden and not the positive ones, while fighting spirit moderated the relationship between somatic symptoms burden and their overall impact on a cognitive, affective and behavioral level, suggesting a potential protective factor in the relationship between SSS-8 and SSD-12.

Previous research has proved that psychological distress can exacerbate somatic symptoms in patients with cancer [32]. Also, somatic symptoms were highlighted to have mediating effects between psychological distress and quality of life in patients with cancer, while screened-positive SSD patients represented a significant predictor of lower quality of life (QOL) ($B = -0.476$, $p < 0.00$) [33]. Also, previous studies reported somatic symptoms as being risk factors for cancer patients' prognosis using the same psychometric tool of SSD-12 but without an emphasis on mental adjustment mechanisms [34]. Moreover, research reported greater psychological adaptation and maturity in coping mechanisms are associated with lower levels of somatic symptoms and depression in patients with cancer [35]. Also, maladaptive emotional responses to cancer, characterized by strong associations between emotional and somatic symptoms, can lead to higher levels of somatization and poorer quality of life in patients with cancer [36]. To our knowledge, until now, no other study explored mental adjustment to cancer mechanisms in relationship with somatic symptoms and their burden.

Concerning specific mental adjustment to cancer mechanisms, previous research linked positive and negative affect to fatalism and fighting spirit with fighting spirit being negatively correlated to fatalism and negative affect [12,37], while another study highlighted anxious preoccupation as a predictor for significant decreases in all the domains of quality of life, with helplessness-hopelessness predictor for significant decreases in emotional and functional wellbeing domains [38].

We showed the strong association between helplessness and somatic symptoms suggesting that patients who feel more overwhelmed and powerless by their illness are more likely to report physical symptoms. Similarly, anxious preoccupation, characterized by excessive worry about the disease, may lead to heightened awareness and reporting of somatic symptoms. An interesting finding of our study relies on fighting spirit as an adaptive mechanism that moderates the relationship between somatic symptoms and overall impact on patients with low and medium values, having a positive correlation that disappears at the highest levels. This may explain fighting spirit as a protective factor in the relationship, an aspect worth considering in modern psycho-oncological approaches and in accordance with previous research on its link to positive affect [39]. The absence of significant effects for adaptive mechanisms in our sample may be attributed to the homogeneity of the sample, particularly regarding cancer type and stage, as well as potential measurement limitations of the Mini-MAC scale in capturing nuanced coping responses. These findings align with literature suggesting that adaptive mechanisms may exert more influence during acute or early-stage illness phases and less during chronic or long-term survivorship. However, our results contrast with studies reporting sustained benefits of fighting spirit over time. This discrepancy highlights the need for future research to explore these mechanisms in more diverse and heterogeneous patient populations and consider longitudinal designs to capture temporal changes in coping efficacy. Tailored interventions that account for individual patient contexts and preferences may be more beneficial than a one-size-fits-all approach focusing solely on adaptive mechanisms like fighting spirit [40].

Concerning somatic symptoms assessment, although the SSD-12 and SSS-8 have good reliability and validity, they cannot replace the diagnostic accuracy of a psychiatric interview. Our descriptive results obtained from this study for both SSD-8 and SSD-12 need to be interpreted appropriately. For many diagnoses, the DSM-5 requires that symptoms from SSD should not be the results of an underlying organic cause [41]. For patients with a medical condition such as cancer, this criterion is not realistic as symptoms may indeed be associated with both the underlying medical condition [42].

Somatic symptom identification in patients with cancer needs more attention to be paid to the psychological care of patients with physical symptoms. However, the observed relationship between mental adjustment mechanisms, such as fighting spirit, and somatic symptoms could be influenced by several confounding variables not fully controlled in our study. For instance, time since diagnosis may alter the effectiveness of coping strategies, with recently diagnosed individuals potentially exhibiting more distress and somatic symptomatology compared to long-term survivors who have developed adaptive coping mechanisms. Additionally, the type and intensity of treatment—particularly chemotherapy and radiotherapy—can exacerbate physical symptoms like fatigue and cognitive impairment complicating the assessment of psychological coping. Furthermore, the disease stage significantly impacts psychological well-being and symptom burden, with advanced stages often associated with higher levels of distress and lower fighting spirit. These

confounders could attenuate or amplify the observed relationships between mental adjustment and somatic symptoms, suggesting the need for future studies to incorporate these variables more comprehensively into their analytical models in order to disentangle their effects.

Therefore, it is necessary to conduct a comprehensive assessment of the patient`s psychological dimensions of the clinical presentation. Hence, we hope to present the phenomenon of somatic symptom prevalence as a consequence of poor mental adjustment mechanisms in patients with cancer, thus highlighting the need to consider this issue by both oncologists and psychiatrists [43,44].

Clinical Implications

Somatic symptoms can be as easily confusing as physical symptoms in this specific type of population, which results in both overmedication and insufficient psychosocial care. In our study, we demonstrated a significant correlation between somatic symptoms and maladaptive mental adjustment mechanisms, a finding that should warrant greater attention to this unique issue among patients with cancer. Identifying patients with high levels of helplessness and anxious preoccupation can help Psycho-oncologists target interventions to reduce it. Psycho-oncology programs focusing on enhancing coping skills and reducing anxiety may be beneficial in this regard for Romania and other countries as costs for invasive and time and financially resources consuming investigations may overwhelm an already limited and insufficiently developed multidisciplinary approach, which may lead to confusion and medical shopping among patients [3].

Limitations

Several limitations should be acknowledged. This was a cross-sectional study, which was unable to determine the causal relationship between mental adjustment mechanisms and somatic symptoms. We selected a single cancer department, including only one hospital from one area in the country, which may limit the generalizability of the findings considering the relatively small sample size. The patient population from this hospital may not be representative of the broader population of patients with cancer in other regions or countries considering factors such as regional healthcare practices, socioeconomic status, higher in Bucharest region, and cultural differences [2,45,46]. Also, the gender imbalance significantly limits the generalizability of the findings, especially for male cancer patients. Studies incorporating larger and more diverse cancer samples, as well as longitudinal studies, are recommended to further understand the relationship between previously described variables. In this study, a formal power analysis was not conducted prior to data collection. Given the complexity of the moderation analyses, particularly in examining the role of 'fighting spirit,' the current sample size of 88 participants may not provide sufficient power to detect small to medium interaction effects reliably. This limitation should be considered when interpreting the findings, as true moderating effects may not have been detected due to insufficient statistical power. Future research should aim to recruit larger samples and conduct a priori power analyses to ensure adequate power for detecting moderation effects. Many patients have more than one concomitant disease, especially advanced patients with cancer and those who have received or are undergoing conventional anticancer treatments. However, we collected information on all somatic symptoms but did not distinguish between symptoms derived from cancer, those derived from treatments and those that resulted from other illnesses. We would like to consider this issue in our future studies on somatic symptoms in cancer populations.

Future directions

Research on patients with cancer focusing on somatic symptoms is still scarce. Most of the studies remain in the stage of presenting descriptive outcomes. More research on the mechanism of somatic symptoms in cancer, whether it has a profound impact on quality of life or survivorship, how to identify it properly and in a timely manner, and which kind of psychosocial interventions would be more effective are necessary in the future. This is the first study to explore how mental adjustment to cancer may predict and moderate somatic symptoms and its burden in Romania and beyond. Future research should consider longitudinal designs to establish causal relationships between the described variables. Studies involving diverse cultural groups are also needed to explore the generalizability of these findings, considering the cultural aspect of somatic symptoms an important point to consider. Furthermore, investigating the effectiveness of psychological interventions in reducing maladaptive adjustment mechanisms would be a valuable contribution to the field of Psycho-Oncology**.**

CONCLUSION

In conclusion, this study highlights the significant relationship between mental adjustment mechanisms as predictors of somatic symptoms in patients with cancer. Considering the intricate nature of somatic symptoms and targeting through Psycho-oncologic interventions, helplessness, anxious avoidance, and fatalism while also exploring fighting spirit may help mitigate somatic symptoms and improve overall well-being in this population, leading to high-quality care for patients.

Conflicts of interest and sources of funding

The authors declare no conflict of interest.

Authors' contribution

Conceptualization, M.L., C.G.I. and L.S.; methodology, L.S.; software, D.M.P.; validation, M.L.., O.V., and A.C.; formal analysis, D.M.P.; investigation, L.S.; resources, M.L.; data curation, C.G.I.; writing—original draft preparation, C.G.I.; writing—review and editing, M.L. and A.C.; visualization, O.V.; supervision, M.L.; project administration, L.S.; funding acquisition, M.L. All authors have read and agreed to the published version of the manuscript.

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Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of Elias Emergency and University Hospital, Bucharest, Romania (nr. 9286/2023).

Patient consent for publication

Informed consent was obtained from all subjects involved in the study.

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ARTICLE

The Neurocardiogenic Impact of Ischemic Stroke: Intricacies of Cardiac Enzymes and the Vegetative System

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Abstract: There is a potential lateralization of vegetative influences at the cerebral level. We sought to understand the impact of these influences in the setting of ischemic stroke. We conducted a prospective study on 110 who presented with acute ischemic stroke (symptom onset maximum 24 hours before admission). We investigated correlations between stroke subtype, insular location or lateralization, stroke severity, hospital mortality, and the dynamic of enzymes (Tn, TnT, CK, CK-MB). We demonstrated that a higher cardiac enzyme value is associated either with stroke severity or with a higher risk of death in the short term, this growth being a marker for a more severe prognosis of a large stroke rather than an independent cause of mortality. Cardiac monitoring in the acute phase of ischemic stroke can prevent cardiac morbidity and mortality, which is why it is important to identify patients at high risk of heart complications after stroke.

Keywords: stroke; vegetative system; cardiac enzymes

INTRODUCTION

The brain structures involved in cardiac autonomic activity regarding the modulation of the force of contraction, heart rate, and stress response are the anterior cingulate cortex, the parabrachial nucleus, the hypothalamus (the paraventricular nucleus, the dorsomedial nucleus, the lateral hypothalamic area), insula (especially its anterior portion), periaqueductal gray matter, and some parts of the medulla (ventrolateral rostral medulla, nucleus ambiguus, nucleus of the solitary tract) [1].

Right insular lesions lead to increased parasympathetic activity to the detriment of sympathetic activity, and the opposite occurs in left insular lesions [2]. Thus, it can be stated that there is a lateralization of vegetative influences at the cerebral level. This lateralization hypothesis applies to the intrinsic control of the cardiac vegetative system [3].

In a study of approximately 865,000 patients, it was observed that the incidence of acute myocardial infarction (MI) in patients with acute stroke reaches 1.6% (approximately 80% being non-STEMI and 20% STEMI). Advanced age is the strongest predictor of MI in stroke patients, along with ischemic heart disease, chronic kidney disease (CKD), and atrial fibrillation (AF) [4,5]. In the trial RANTTAS [6], it has been observed that in 6% of acute ischemic strokes, cardiac complications may occur, such as angina pectoris, acute MI, and cardiac ischemia. Cardiac monitoring is crucial after a stroke. Prolonged cardiac monitoring is a weak link in stroke care in Romania overall – evaluation past the first 24-48 hours is a rarity [7]. Acute MI after stroke may have the following etiopathogenic mechanisms: concomitant coronary artery occlusion or exacerbation of a pre-existing coronary artery disease secondary to excessive and abnormal catecholamine discharge in the acute phase of stroke [4,8,9]. Sympathetic hyperactivity in the acute phase of stroke leads to excessive stimulation of beta receptors, with the opening of Ca^{2+} channels with the intracellular flow of Ca^{2+}, contractile myocardial dysfunction, and ATP depletion, leading to mitochondrial dysfunction, and finally, cell death, translated into the paraclinical image of ECG changes and increased troponin (Tn) values [10].

In patients with acute ischemic stroke, myofibrillar degeneration, myocytolysis or the appearance of contraction band necrosis may occur, the death of myocardial

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cells occurring in a state of exaggerated contraction, followed by the rapid appearance of calcifications and infiltration of mononuclear cells. In contrast, in acute MI, the important occurrence of necrosis contraction bands is not identified, and the process of necrosis of myocardial cells takes hours - days, occurs in a state of relaxation, and calcifications are delayed. Thus, neurogenic myocytolysis involves the subendocardium with a high arrhythmogenic potential, different from the coagulative necrosis encountered in acute MI [11]. Scheiz et al. [12] proposed a method of classifying Tn growth in patients with acute stroke into two categories: patients with an acute Tn increase and patients with a chronic Tn increase. In those with an acute troponin (Tn) increase, after excluding acute MI, it was observed that, most likely, this increase is the consequence of neurogenic lesions.

MATERIALS AND METHODS

Patients selection

We conducted a prospective study on 110 patients hospitalized in the Neurovascular Emergency Unit who presented with acute ischemic stroke (symptom onset taking place a maximum of 24 hours before admission). We excluded patients with:

- Ischemic stroke with onset >24 hours before admission
- Hemorrhagic stroke
- The presence of simultaneous acute pulmonary edema
- Clinical and laboratory signs of simultaneous acute myocardial infarction
- History of MI in the last year
- Recent cardiac surgery (<1 year)
- History of severe CKD (terminal stage)
- History of lung disease with severe acute respiratory failure
- History of clinically relevant arrhythmias (especially atrial fibrillation)
- Advanced cardiac insufficiency (Stage III/IV NYHA)
- History of active malignancy

Objective

The study's objective was to highlight the correlation between enzymatic changes (their dynamic during the first five days after stroke onset) and insular involvement/insular lateralization, stroke etiology, severity of acute ischemic stroke (using the NIHSS score at admission and at seven days), and in-hospital mortality.

Data collection

Before inclusion in the study, patients were informed about the methodology and the clinical, paraclinical, imaging, and other explorations performed. Each patient (or caregiver if the patient has severe language disorder, impaired understanding, cognitive impairment, or impaired alertness) has signed informed consent, respecting the conditions of medical ethics. The approval of the Scientific Research Ethics Board of the University of Medicine and Pharmacy "Carol Davila" Bucharest, Romania, was obtained for this study.

Etiological diagnosis of stroke

The etiological diagnosis of stroke was performed using the TOAST classification [13] after paraclinical tests (brain CT / MRI, Doppler ultrasound, standard ECG, 24-hour Holter monitoring, 5-day continuous ECG monitoring, and transthoracic echocardiogram).

Stroke severity

The clinical severity of ischemic stroke was calculated using the NIHSS (National Institutes of Health Stroke Scale) by a neurologist certified to use the NIHSS scale. According to the NIHSS scale, stroke patients were divided into 3 categories:

- mild stroke (NIHSS ≤8 points)
- moderate stroke (NIHSS = 9-15 points)
- severe stroke (NIHSS ≥16 points).

Statistical methods and statistical calculation tools

For both Tn and creatine-kinase MB (CK-MB) values, the Kolmogorov-Smirnov normality test (which determines to what extent the data have a normal/Gaussian distribution) was applied, which invalidated normality, which is why the Student t-test could not be applied. We resorted to a non-parametric test, Mann-Whitney (MW), which demonstrated the absence of a significant difference between troponin/CK-MB values on any 2 days (of the 5 days studied). The Mann-Whitney test was used to analyze the correlation

between stroke subtype, insular location/insular lateralization, stroke severity, hospital mortality, and enzymatic elevations (Tn, TnT, CK, CK-MB). The chi-squared test was applied to investigate the possible correlation between increased values of myocardial lesion indicators (choosing those with a higher cardiac specificity: TnT and CK-MB) and acute ischemic stroke.

RESULTS

Etiology, risk factors and demographic factors of patients

The mean age of the patients was 67.2+/-12.93 years, and the male-to-female ratio was 64.55%:35.55%. The prevalence of vascular risk factors and associated pathologies was the following – high blood pressure (HBP) 73.64%, obesity 31.82%, diabetes 23.64%, dyslipidemia 46.36%, active smoking 50%. Chronic alcohol usage was recorded in 27.27% of patients, stroke history in 21.82%, transient ischemic attack (TIA) in 1.82%, heart failure (HF) NYHA class 1 or 2)= in 5.45%, past MI in 8.18%, dementia in 10%, peripheral arteriopathy in 3.64%, chronic obstructive pulmonary disease in 1.82%, CKD (stage 1 or 2) in 0.91% of patients. Death during admission occurred in 14 of 110 patients (12.72%).

The etiological classification of stroke was performed based on the TOAST system criteria (Trial of Org 10172 in Acute Stroke Treatment) [13] in cardioembolic (29.09%), atherosclerosis of large vessels (50.90%) [including a small proportion atheroembolic (6.36%)], lacunar (3.64%), other causes (internal carotid artery dissection 1.81%) and cryptogenic (14.54%).

Insular localization of ischemic stroke and insular lateralization

Regarding the topographic location of stroke, out of the total of 110 patients included in the study, 63 patients (42.73%) had a stroke located in the insula. Of the 63 patients with insular localization, 23 patients (36.5%) had right insular localization and 40 patients (63.5%) had left insular localization.

The growth dynamic of cardiac enzymes was analyzed. There was no sustained increase in cardiac enzymes during the 5 days of follow-up. In all calculations concerning cardiac enzymes, the 3 patients who were found to have had acute MI after stroke onset were excluded.

Patients were divided into 2 categories according to Tn T levels: patients with normal values (≤0.02ng/ml) and patients with values above the upper limit (>0.02ng/ml). A similar division of patients was performed according to the CK-MB value: patients with normal values (≤25IU/L) and patients with superior values (>25IU/L). Following this analysis, it was observed that out of the total 110 patients, 60.86% had at least one elevated TnT value (in at least one of the 5 days of follow-up) (Figure 1), and 36.52% had at least one increased CK-MB value (in at least one of the 5 days of follow-up) (Figure 2).

For each patient, we took into consideration the highest value obtained in the 5 days of follow-up. The relatively high percentage of patients with elevated TnT is within the limits demonstrated in the literature, in a review [14] on increased Tn in patients with acute stroke (ischemic and hemorrhagic), this percentage difference is pending on various factors, such as the chosen day of reference, the number of patients and the arbitrary baseline. When applying the chi-squared test to analyze the correlation of TnT value above the normal limit of every 5 days with insular localization, on day 4 and 5, the TnT value correlation with insular involvement was statistically significant (Table 1). No statistically significant correlation with insular lateralization was observed. The increase in Tn (less specific for cardiac distress than TnT) did not correlate with insular involvement nor with left-right insular lateralization.

Figure 1: The distribution of TnT values in the studied group

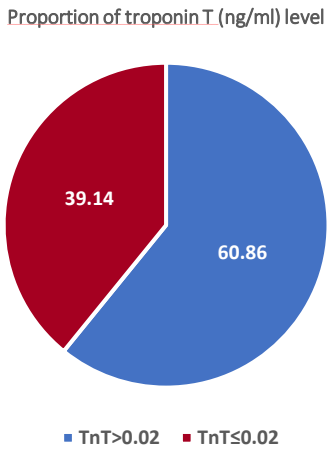

Figure 2: The distribution of CK-MB values in the studied group

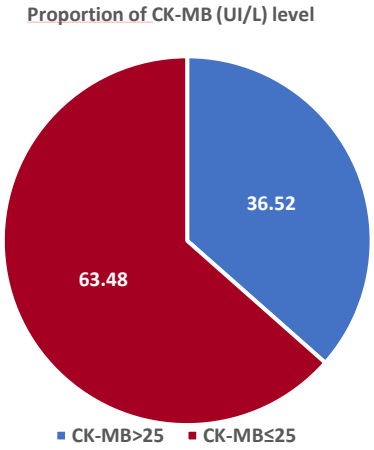

Table 1: TnT value and stroke location

Parameter	Insular	Non-insular	P-value
TnT day 4, [median (Q1-Q3)]	0.029(0.01-0.029)	0.01(0.01-0.029)	0,007 (Mann-Whitney)
TnT day 5 [median (Q1-Q3)]	0.029(0.01-0.029)	0.01(0.01-0.029)	0,02 (Mann-Whitney)

On average, CK-MB was significantly higher in patients with insular localization on each follow-up day (day 1 to day 5) (Table 2), but this was not statistically significant depending on insular lateralization. There was also no statistically significant correlation between insular location or insular lateralization and the CK value.

Table 2: CK-MB value related to stroke location

Parameters	Insular	Non-insular	P-value
CK-MB day 1, [median (Q1-Q3)]	17 (14-23)	14 (12-16)	0.006 (Mann-Whitney)
CK-MB day 2, [median (Q1-Q3)]	17 (13,21.5)	13 (11-15.25)	0,0004 (Mann-Whitney)
CK-MB day 3, [median (Q1-Q3)]	16.25 (13.25,20.75)	14 (11.25-17.75)	0,03 (Mann-Whitney)
CK-MB day 4, [median (Q1-Q3)]	19 (13.75-26.25)	13 (12-16)	0.0002 (Mann-Whitney)
CK-MB day 5, [median (Q1-Q3)]	16 (13-18.75)	13 (10.25-15)	0,003 (Mann-Whitney)

Stroke subtypes and cardiac enzymes

Regarding stroke etiology, a statistical correlation between stroke subtype and an increase in CK-MB or TnT during any of the 5 days of follow-up has not been demonstrated (neither by the Mann-Whitney test nor by the Chi-Square test).

Stroke severity and cardiac enzymes

When analyzing the correlation between stroke severity and cardiac enzyme elevations, the mean CK-MB on days 2, 3, 4, and 5 was statistically significantly higher in patients with severe stroke (NIHSS score ≥16) than in patients with moderate and mild stroke (NIHSS<16). CK (day 3 and 4) and Tn (day 4) were, on average, statistically significantly higher in patients with severe stroke than in patients with moderate to mild stroke (Table 3). TnT, much more sensitive for myocardial injury, did not record statistically significantly higher values in patients with severe stroke.

Table 3: Correlation between cardiac enzymes and stroke severity

Parameters	NIHSS<16 (moderate stroke)	NIHSS≥16 (severe stroke)	P-value
Tn day 4, [median (Q1-Q3)]	0.2 (0.2-0.2)	0.2 (0.2-0.26)	0.003 (Mann-Whitney)
CK day 3, [median (Q1-Q3)]	91 (51.9-139)	132 (82-254)	0.001 (Mann-Whitney)
CK day 4 (median (Q1-Q3))	100 (59-147)	115.5 (71.75-296)	0.004 (Mann-Whitney)
CK-MB day 2, [median (Q1-Q3)]	13 (12-16)	17 (13-20.75)	0.002 (Mann-Whitney)
CK-MB day 3, [median (Q1-Q3)]	14 (12-18)	17 (13-21)	0.002 (Mann-Whitney)
CK-MB day 4, [median (Q1-Q3)]	15 (12-19.5)	18.5 (13.75-26.25)	0.002 (Mann-Whitney)
CK-MB day 5, [median (Q1-Q3)]	13 (11-16)	15.5 (13-18.25)	0.002 (Mann-Whitney)

Cardiac enzymes and mortality

The correlation between enzyme increases and in-hospital mortality was analyzed. For Tn, a statistically significant correlation was observed between its increase on days 3, 4, 5 and hospital mortality. TnT on day 4 was, on average, significantly higher in patients who died during hospitalization than in those who survived. The increase in CK and CK-MB on days 4 and 5 correlated significantly with death during hospitalization (Table 4).

Table 4: Correlation between enzyme values and in-hospital death

Parameters	Death	No death	P-value
Tn day 3 [median (Q1-Q3)]	0.378 (0.2-1.129)	0.2 (0.2-0.2)	0,01 (MW)
Tn day 4 [median (Q1-Q3)]	0.506 (0.31-1.33)	0.2 (0.2-0.2)	0.002 (MW)
Tn day 5 [median (Q1-Q3)]	0.426 (0.26-0.81)	0.2 (0.2-0.2)	0,009 (MW)
TnT day 4 [median (Q1-Q3)]	0.049 (0.02-0.2)	0.01 (0.01-0.03)	0,008 (MW)
CK day 4, median (Q1, Q3)	326 (180.75-1621)	101 (61-177)	0,02 (MW)
CK day 5 [median (Q1-Q3)]	15 (188-4468)	288 (55.5-160)	0,01 (MW)
CK-MB day 4 [median (Q1-Q3)]	38 (21.5-55.75)	16 (12-20)	0.006 (MW)
CK-MB day 5 [median] (Q1-Q3)]	29 (19-63)	14 (12-17)	0,01 (MW)

MW=Mann-Whitney

DISCUSSION

With regard to the growth dynamics of cardiac enzymes, a time-based increase was not observed as in other studies [15]. No statistical correlation has been demonstrated (either by the Mann-Whitney test or by the chi-square test) between the stroke subtype and CK-MB or TnT elevation on any of the 5 follow-up days.

The increase in myocardial injury indicators has been interpreted differently in existing studies, with some authors considering it a marker of stroke severity and not an independent factor of poor prognosis [16] and others see it as an independent predictor of disability or mortality [17,18]. Apart from the current study, the literature has revealed only one study [19] that previously targeted the timed growth (days 1, 2, 3, 4, 5) of cardiac enzymes in stroke patients; other studies chose a variety of values of cardiac enzymes.

The possible pathophysiological mechanisms of increasing TnT and CK-MB in patients with acute stroke are multiple, but none of the studies existing so far in the literature could establish the exact cause. There is evidence of neurocardiogenic influences on myocytolysis in the acute phase of stroke, but there is great controversy regarding the cardiogenic increase in CK-MB. This increase may be possible in the case of a stroke location with a high potential for heart damage. Supporting the theory of a cardiac CK-MB increase secondary to neurogenic influences, in our study, 36.52% of patients had values above the normal limit of CK-MB, and the value of CK-MB (and TnT) correlated with insular involvement.

The current study offers different results than other literature references [20] - which concluded that TnT, unlike CK-MB, does not increase in patients with acute ischemic stroke. Also, the current study demonstrates contradicting conclusions to Barber et al. [21], which showed that in patients with acute ischemic stroke and elevated TnI, this increase did not correlate with insular location, one explanation being that in the cited study, only one TnI value was measured upon admission, whereas in the current study, statistically significant results were obtained on day 4 and 5 from stroke onset. Other examples from the literature [22] demonstrated a correlation between increased TnI and right hemisphere ischemia, but no insular involvement was specified, and no differences in insular lateralization were observed. One explanation could be that this increase is not related to other brain locations except insular ones, although further studies on other brain locations will need to be conducted to prove this claim. An argument against the theory mentioned above would be that the results obtained are controversial when it comes to the correlation of TnT alone with cardiac function, which makes it possible that CK-MB increase is not of cardiac origin and demonstrates that TnT is a much more reliable parameter to highlight the cardiac impact of chronic ischemia.

The statistical significance of elevated TnT and CK-MB values at days 4 and 5 with insular location may actually be due to a large ischemic stroke, and the increased TnT may reflect the systemic severity of stroke that may worsen the neurological status. A possible pathophysiological mechanism would be that in the case of large ischemic strokes, the growth curve of cerebral edema is maximum on days 4-5-6 from the onset of cerebral ischemia. Cerebral edema during these days may cause an exacerbation of sympathetic activity; this explanation is supported in a previous study [15], which revealed that CK-MB values are higher on day 5 of stroke onset. Obviously, this hypothesis will require further research in the future, by measuring catecholamines and enzymes simultaneously. Increased CK-MB value may originate elsewhere (muscle damage due to venous punctures, fluid restriction, and negative caloric

intake) [20]. In support of this argument comes the association of growth and CK.

In fact, it is well known that TnT is much more sensitive for assessing cardiac ischemia, either acute or chronic. The authors are of a similar opinion to the study conducted by Jensen et al. [18] that the increase in TnT is rather the consequence of HF. Another plausible explanation for the increase in TnT could be the existence of unstable atheroma plaques in the coronary arteries that could cause recurrent myocardial ischemia. It is probably necessary to dose other types of Tn (hsTnI) to correctly evaluate cardiac myocytolysis in patients with acute ischemic stroke and to redefine the concept of neurogenic cardiac ischemia.

Although this study cannot accurately state the pathophysiology of the increase in cardiac enzymes, we demonstrated that a higher value is associated either with stroke severity or with a higher risk of death in the short term, this growth being a marker for a more severe prognosis of a large stroke rather than an independent cause of mortality.

Looking at cardiac enzymes, the value of TnT and CK-MB was related to stroke severity, which indicates that in well-selected cases cardiac enzyme dosing may be useful for stratifying the risk of cardiac complications. It cannot be stated that the dosing of TnT and CK-MB should be performed routinely in all patients with acute stroke, being an expensive method and not providing additional net benefit**.**

CONCLUSION

Cardiac complications are common in patients with acute ischemic stroke, some of which may be potentiated by autonomic hyperactivity. Careful monitoring of patients at high risk of heart complications may change the short-term prognosis.

Conflicts of interest and sources of funding

The authors declare no conflict of interest. This research received no external funding.

Authors' contribution

Conceptualization and design, MMM, DD, ST; data analysis, MMM, DD; preparing the manuscript, MMM, IIE, ICS, MIG, OV, ST, DD, CV, CAS; writing, review and editing, MMM, DD.; visualization, MMM, DD; supervision, MMM. All authors have read and agreed to the published version of the manuscript.

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The current manuscript does not contain previously published materials or self-generated AI text.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of "CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY (protocol code PO-35-F-03 no. 83 and date of approval: 29.02.2016).

Patient consent for publication

Written informed consent has been obtained from the patient(s) to publish this paper.

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REVIEW

Radiotherapy and Reconstructive Surgery: Challenges, Implications and Optimized Therapeutic Approaches

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Abstract: Radiotherapy plays an indispensable role in cancer treatment, with its ability to target malignant cells and improve patient survival. However, its impact on healthy tissues poses significant challenges for reconstructive surgery. The altered tissue environment resulting from radiation, including fibrosis, vascular damage, and compromised wound healing, complicates reconstructive efforts and increases the risk of surgical complications. As cancer therapies advance, the approaches for managing radiation-induced complications must also adapt accordingly.

This article explores the complex interaction between radiotherapy and reconstructive surgery, particularly in the treatment of head and neck cancers, breast reconstruction following mastectomy, and sarcoma management. Special attention is given to the customization of surgical approaches based on cancer type, with the goal of optimizing both functional and aesthetic outcomes. A multidisciplinary approach, integrating advanced imaging techniques, modern radiation delivery methods, and innovative surgical techniques is essential for improving patient outcomes.

Keywords: radiotherapy, reconstructive surgery, head and neck cancer, breast reconstruction, sarcoma

INTRODUCTION

Radiotherapy is an essential part of therapeutic management, utilized in approximately 50-60% of all cancer patients during their treatment. It plays an important role in controlling tumor growth, reducing recurrence rates, and improving overall survival. However, despite its therapeutic efficacy, radiotherapy can have serious adverse effects on surrounding healthy tissues, leading to complications such as fibrosis, vascular damage, and impaired wound healing. These radiation-induced changes significantly complicate subsequent reconstructive surgery, particularly in areas where structural architecture and functional restoration are critical. [1-3]

The association between radiotherapy and reconstructive surgery presents unique challenges, especially in cases of head and neck cancers, breast cancer treatment, and sarcomas. This article aims to explore the impact of radiotherapy on reconstructive surgery, focusing on these three specific cancer types, the final goal being to optimize both functional and aesthetic outcomes for cancer survivors.

OVERVIEW OF PARTICULAR SITUATIONS REGARDING RADIOTHERAPY AND RECONSTRUCTIVE SURGERY

Head and neck cancer treatment

Head and neck cancers are frequently treated with radiotherapy, either as a primary modality or adjuvant therapy following surgery. While radiotherapy effectively targets malignant cells, it also damages surrounding healthy tissues, leading to fibrosis, vascular compromise, and wound healing complications. [4] Novel strategies for improving radiotherapy protocols are currently being explored. In the case of radioresistant tumors, for head and neck oncological cases, proton and carbon ion therapies are emerging as superior options. Proton therapy facilitates the delivery of high-dose radiation accurately, concurrently preserving adjacent healthy tissue, thereby rendering it appropriate for the eradication of microscopic disease.

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Carbon ion therapy, with its higher linear energy transfer, is more effective for larger tumors with significant burdens, offering enhanced biological effectiveness in tumor cell damage. [5]

For locoregional recurrences or second primary malignancies, reirradiation (RERT) with advanced techniques like intensity-modulated radiation therapy (IMRT) and stereotactic body radiotherapy (SBRT) is a viable option. These methods improve survival rates and reduce toxicity by precisely targeting the tumor while sparing normal tissues. [6]

Intraoperative Radiation Therapy (IORT) has been described to be efficient when utilized alongside surgical procedures. IORT provides a targeted radiation boost during surgery, potentially reducing the need for high doses of external beam radiation and minimizing exposure to normal tissues, particularly beneficial in recurrent cases where additional radiation is required. [7]

Radiotherapy in the head and neck region presents several unique challenges. One of the primary concerns is fibrosis and soft tissue contracture; radiation induces progressive fibrosis, which can result in trismus, dysphagia, and restricted neck mobility. Soft tissue contracture can further complicate flap elevation and wound closure. Compromised vascularity is another challenge, as radiotherapy damages the microvasculature, leading to poor perfusion and an increased risk of flap necrosis. Additionally, the complex anatomy of the head and neck region, which includes multiple vital structures such as the facial nerve and carotid artery, makes surgical navigation particularly challenging. [7-11]

To address these challenges, several surgical strategies are currently employed. Reconstructive surgery after head and neck cancer aims to restore function, appearance, and quality of life. Free tissue transfer, utilizing free flaps such as the anterolateral thigh (ALT) flap or radial forearm flap, remains a mainstay due to their robust vascularity and versatility. Preoperative imaging modalities like CT angiography or MR angiography are crucial for assessing recipient vessel patency and planning the anastomosis. In cases where free flap transfer is not feasible, pedicled flaps, such as the pectoralis major myocutaneous flap, provide reliable coverage. Additionally, functional reconstruction, including dynamic reconstruction of facial nerve function using gracilis muscle transfer and nerve grafts, is performed to restore facial symmetry and expression. [11-14]

Emerging techniques in this field show promise for improving outcomes. For mandibular reconstruction, the fibula flap remains the gold standard, followed by scapular flaps in selected cases; however, recent advancements in 3D printing technology have enabled the creation of custom-made implants, which can enhance functional outcomes. Despite their effectiveness, free flaps carry a higher risk of complications, such as pedicle thrombosis, especially when using irradiated vessels. [13,15-17]

Breast Reconstruction after breast cancer

Breast cancer is the most common malignancy among women and the leading cause of cancer-related mortality in females. [18,19] Surgical options for breast cancer treatment generally include breast-conserving therapy associated with radiotherapy or mastectomy, both of which offer comparable survival rates for patients with early-stage disease. [18,20] With the advent of magnetic resonance imaging (MRI), BRCA-1 and BRCA-2 genetic screening, and advancements in surgical techniques, mastectomy followed by reconstruction has become an increasingly preferred treatment option. [18] For patients undergoing mastectomy with reconstruction, a decision must be made between autologous tissue reconstruction and implant-based reconstruction. Both approaches can be performed either immediately following the mastectomy or at a later stage. Radiotherapy is recommended for high-risk cases, significantly increasing the complication rate associated with any type of reconstruction. [18,21-23]

Breast reconstruction after radiation therapy is a challenging process that aims to restore the breast's appearance while managing a series of adverse effects introduced by radiation. [24]

Deciding on the type of breast reconstruction involves a thorough discussion between the patient and her reconstructive surgeon, focusing on the expected outcomes and potential complications. Autologous reconstruction, which uses the patient’s own well-vascularized soft tissue, closely resembles natural breast tissue, can be easily shaped, and generally yields more natural-looking results. Moreover, autologous reconstruction is known to be more resilient to the effects of post-mastectomy radiation therapy (PMRT). [25,26]

A significant challenge in breast reconstruction, particularly for patients who have received or will receive radiation therapy, is determining the optimal timing for reconstruction. Radiation therapy, while crucial for reducing the risk of cancer recurrence, can complicate reconstruction efforts. Post-mastectomy radiotherapy is a common treatment that can reduce local recurrence rates and improve survival, especially in patients with lymph node-positive breast cancer. However, PMRT can negatively impact the outcome of flap reconstructions, leading to complications such as flap loss, wound contracture, and fat necrosis. [27-30]

Breast reconstruction using autologous tissue is favored because it results in a more natural-looking breast with a soft texture, consistent temperature, and a certain degree of ptosis that closely mimics the natural breast. Furthermore, autologous tissue is more resilient to the effects of radiation therapy, making it a suitable option for patients who have undergone or will undergo radiation. Autologous reconstruction is considered the gold standard by many plastic surgeons due to its superior aesthetic outcomes and the fact that it allows the reconstructed breast to age naturally alongside the other breast. It is also more customizable, enabling surgeons to tailor the reconstruction to the individual patient's needs. [31-34]

Multiple flap options are available for breast reconstruction, each tailored to meet specific patient anatomical considerations and reconstructive goals. The latissimus dorsi myocutaneous (LD) flap remains a versatile and reliable choice, particularly in cases where moderate tissue volume is required. Abdominally-based flaps, such as the transverse rectus abdominis myocutaneous (TRAM) flap,

deep inferior epigastric perforator (DIEP) flap, and superficial inferior epigastric artery (SIEA) flap, are considered the gold standard for autologous breast reconstruction due to their abundant soft tissue, robust vascularity, and the potential to achieve highly natural aesthetic outcomes. Thigh-based flaps, including the transverse upper gracilis (TUG), transverse myocutaneous gracilis (TMG), profunda artery perforator (PAP), and lateral thigh perforator (LTP) flaps, provide valuable alternatives for patients who are unsuitable candidates for abdominal donor sites, offering well-vascularized tissue with satisfactory volume and contour. Gluteal flaps, such as the superior gluteal artery perforator (SGAP) and inferior gluteal artery perforator (IGAP) flaps, are particularly beneficial in cases where other donor sites are not viable or in patients requiring a larger volume of tissue. The thoracodorsal artery perforator (TDAP) flap and lumbar artery perforator (LAP) flap represent additional options for autologous breast reconstruction, particularly in cases where more conventional donor sites are unsuitable. [35-46]

Two main strategies exist for combining flap reconstruction with radiotherapy: immediate reconstruction, where the reconstruction is performed immediately after the tumor is removed and before radiation therapy, and delayed reconstruction, where radiation is completed first, and reconstruction is performed 6-12 months later. Immediate reconstruction has the advantage of preserving the breast envelope, making the surgery easier and potentially resulting in better aesthetic outcomes. However, it also comes with significant risks. Radiation therapy can cause fibrosis, shrinkage, and fat necrosis in the reconstructed breast, leading to higher rates of complications compared to unirradiated reconstructions. Additionally, complications from immediate reconstruction can delay the start of radiotherapy, which could negatively affect the patient's cancer prognosis. [26,46,47]

Delayed reconstruction, on the other hand, allows the skin and tissues to recover from the effects of radiation before undergoing reconstruction. This approach may reduce the risk of complications but often results in less favorable cosmetic outcomes. The skin and tissues may become fibrotic and scarred, limiting the options for reconstruction and making it harder to achieve a natural breast shape. [48,49]

To minimize radiation injury to the flap while preserving the breast mound, a two-stage approach called delayed immediate autologous reconstruction (DIAR) can be considered. This technique, described by Kronowitz et al., allows for the preservation of the native breast skin and supports the patient’s psychological well-being. DIAR offers the advantages of skin-sparing mastectomy while reducing radiation-induced complications. However, the use of a tissue expander in this method is not without risks. It is debated whether deflating the tissue expander before radiotherapy is necessary. Historically, deflation was thought to give the radiotherapist better control, similar to treating a flat chest. However, more recent studies suggest that deflation is not essential, and keeping the expander inflated may actually reduce radiation-induced complications such as seroma formation and capsular contracture. [50-56]

While autologous reconstruction is often preferred for its aesthetic appeal and lower overall complication rates, prosthetic reconstruction is a practical alternative for some patients. Despite the well-documented increased risks of complications, infections, capsular contracture, the need for revision surgery, and overall reconstruction failure associated with prosthetic reconstruction in the setting of PMRT, it remains an option for a select group of patients. [57,58]

Prosthetic reconstruction, like autologous reconstruction, can be performed in either a single stage or two stages. Single-stage reconstruction, commonly known as direct-to-implant (DTI) reconstruction, involves placing the final implant during the initial surgery. The two-stage approach involves first placing a tissue expander, which is later replaced with a permanent implant. A key debate in prosthetic reconstruction is whether radiotherapy should be administered to the implant or the tissue expander. Recent systematic reviews indicate a significantly higher failure rate when PMRT is delivered to a tissue expander compared to an implant. Although the complication rates are generally lower when using implants rather than tissue expanders, these reviews often overlook the long-term results. Capsular contracture, which can negatively impact patient quality of life and satisfaction with the cosmetic outcome, often does not become apparent until years after the reconstruction. Patients who have previously undergone radiation therapy have the highest rates of reconstruction failure across all groups. Due to the significant morbidity associated with tissue expansion in irradiated skin, pure prosthetic delayed reconstruction is relatively contraindicated. [54,59-63]

Autologous fat grafting, or fat transfer, is frequently used in breast reconstruction, either as a complementary technique or a primary modality. This procedure implies the harvesting of adipose tissue from donor sites such as the abdomen, thighs, or flanks through liposuction, followed by purification and injection into the breast to augment volume, contour, and symmetry. Fat grafting improves the aesthetic results of both flap-based and implant-based reconstructions, addressing contour deformities and enhancing the overall cosmetic outcome. Moreover, fat grafting has demonstrated the capacity to improve the quality of irradiated skin by promoting neovascularization and decreasing radiation-induced fibrosis, providing not only simple volume restoration but also further therapeutic advantages. The grafted fat contains adipocyte-derived stem cells, whose regenerative capacity has been well-documented in various clinical contexts, contributing to improved tissue repair and functional recovery. Although long-term outcomes of fat grafting are still under investigation, current evidence supports its role as a versatile, minimally invasive technique that can significantly improve both the functional and aesthetic results of breast reconstruction. [64-69]

Reverse expansion is a technique used in breast reconstruction after nipple-sparing mastectomy, where a tissue expander is initially inflated to maintain the skin envelope of the breast and to provide adequate coverage for reconstruction. The expander is then gradually deflated, allowing the tissue to contract naturally, resulting in a more contoured and natural breast shape for the final reconstruction. In selected, reverse expansion can be combined with lipofilling to achieve very good outcomes in breast reconstruction, a technique described also as “intratissular expansion with serial deflation–lipofilling sessions”. While reverse expansion helps prepare the tissue and create the necessary space for reconstruction, lipofilling in multiple sessions is used to provide

volume, enhance the aesthetic result, smooth out any irregularities, and improve the quality of irradiated or compromised skin. [70-72]

Radiotherapy in the treatment of breast cancer also increases the risk of secondary lymphedema. A key area of focus is the prevention of lymphedema and the development of advanced therapeutic strategies. These approaches encompass not only conservative management but also cutting-edge super-microsurgical techniques, including the use of robotic microsurgery, to enhance treatment outcomes. [73-76]

These advanced reconstructive options enable the customization of surgical approaches to optimize both functional and aesthetic outcomes in breast reconstruction following mastectomy.

Sarcoma treatment

Sarcomas are highly aggressive tumors that pose a significant risk to patient survival, necessitating prompt and effective treatment. Comprehensive management strategies, including a combination of surgery, radiation therapy and chemotherapy in specific cases, are essential to optimize outcomes and mitigate the high potential for local recurrence and metastasis. Early diagnosis and a multidisciplinary approach are crucial to improving prognosis and reducing the substantial morbidity and mortality associated with these tumors. Radiation therapy plays a crucial role in the management of sarcomas, particularly in cases where surgical resection alone may not achieve optimal outcomes. Given the diverse histological subtypes and varying radiosensitivity of sarcomas, radiation therapy can be tailored to enhance local control, minimize recurrence, and improve overall survival rates. Preoperative radiation is often utilized to reduce tumor size, making surgical resection more feasible while preserving surrounding tissues and critical structures. Conversely, postoperative radiation may be employed to eradicate microscopic residual disease in cases where negative surgical margins are difficult to achieve. [77-79]

Concerns about negative microsurgical outcomes in patients receiving preoperative radiation therapy are justified. Irradiated wounds are described as challenging surgical environments, marked by dense fibrosis, tissue edema, and fragile recipient vessels that are prone to rupture. At the cellular level, in vitro studies have shown that radiation therapy induces cytokine upregulation in the endothelium and accumulation of inflammatory cells. [80,81]

Some studies suggested that a key strategy to successful free tissue transfer is selecting recipient vessels outside of the irradiated field. This is a more practical approach in head and neck reconstruction where there are a plethora of available recipient vessels. However, in limb reconstruction, the irradiated field often spans the entire limb circumference and getting out of the irradiated field may require the use of vein interposition grafts, which themselves can increase free flap failure rate. [82]

Surgical resection with wide margins, combined with perioperative radiation therapy, is the standard treatment for extremity soft tissue sarcomas. [83]

The timing of radiotherapy in the treatment of soft tissue sarcoma remains a topic of debate. Radiation protocols typically include either pre-operative or post-operative external beam radiotherapy, or brachytherapy. Pre-operative irradiation offers several benefits, including the delivery of a lower radiation dose to a smaller field, the potential for tumor downsizing before resection, and improved long-term functional outcomes. However, these advantages are offset by a higher incidence of wound healing complications compared to post-operative radiotherapy. [84]

Intraoperative radiotherapy (IORT) can be employed to enhance margin control by delivering a concentrated dose of radiation (typically 10-12 Gy) to the tumor bed during surgery. This approach is particularly useful when tumors are near vital neurovascular structures or when the resection margin is within several millimeters of the sarcoma. [85]

Regarding microsurgical outcomes, there are additional concerns about the effects of radiotherapy on the quality of recipient vessels, the recipient bed, and ultimately, the survival of the flap. When planning reconstruction for a soft tissue defect, key considerations include the size, location, and depth of the defect. Small-sized defects with a limited zone of injury can be effectively covered using local or perforator-based flaps. For medium-sized defects, axial pattern pedicled flaps are suitable, as they offer a greater reach while still utilizing local tissue.

Large defects, which cannot be adequately covered with local tissue, require distant or free flaps, as these are not constrained by local tissue availability. Locoregional flaps are often effective for reconstructing defects of moderate size. Among these, local fasciocutaneous flaps and pedicled muscle or myocutaneous flaps are viable options. The pedicled rectus abdominis flap, which can be oriented vertically (vertical rectus abdominis musculocutaneous, VRAM), obliquely, or transversely (TRAM), is versatile for reconstructing various defects.

Commonly used muscle flaps include the gracilis, rectus femoris, sartorius, and vastus lateralis. The anterolateral thigh (ALT) flap is the primary fasciocutaneous option, and keystone and freestyle propeller flaps can also be designed for a variety of thigh or truncal defects. For larger defects, the latissimus dorsi (LD) and rectus abdominis are commonly used free muscle flaps, both of which can be harvested with a skin paddle. Additionally, the subscapular and lateral femoral circumflex arterial systems (LFCA) allow for the harvesting of large chimeric flaps for composite tissue replacement when necessary. For reconstructing large defects, the ALT, TRAM, and latissimus dorsi free flaps are excellent choices. For smaller defects, options include the free gracilis, radial forearm, parascapular, lateral arm, and superficial circumflex iliac artery perforator (SCIP) flaps. [86-90].

CONCLUSION

Radiotherapy, while essential for cancer treatment, introduces significant challenges to reconstructive surgery due to the damage it causes to healthy tissues. Advances in radiotherapy techniques, such as proton and carbon ion therapies, offer promising solutions for minimizing damage to surrounding tissues, thereby enhancing reconstructive outcomes. Surgical innovations, including the use of autologous flaps, 3D printing, and intraoperative radiotherapy, have significantly improved the ability to restore function and aesthetics in patients undergoing reconstruction after radiotherapy. However, the complexity of irradiated tissues requires a specific, multidisciplinary approach that takes into consideration the particular needs of each patient and cancer subtype. As reconstructive techniques continue to evolve, further research and collaboration between oncology, radiology, and surgery will be of utmost importance in the improvement of cancer survivors' outcomes.

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ORIGINAL ARTICLE

Multidrug-resistant ESKAPE Pathogens in a Romanian Secondary-Care Hospital during the COVID-19 Pandemic

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Abstract: The study aims to assess the frequency of ESKAPE pathogens and their antimicrobial resistance profile during the COVID-19 pandemic in a multidisciplinary hospital. Based on microbiological reports, the present study retrospectively evaluated the frequency and antimicrobial resistance (AMR) profile of ESKAPE microorganisms during 2020-2022 in a multidisciplinary hospital in Romania. There were reported 1117 bacterial isolates during the study and ESKAPE pathogens account for 33.5% of the strains. The specific AMR of ESKAPE pathogens cumulates 30.9%, while antimicrobial multidrug resistance characterizes 21% of all ESKAPE strains. The AMR profile of K. Pneumoniae, followed by S. aureus, and P. aeruginosa are alarming on ESKAPE surveillance. The most frequent bacterial isolates and antibiotic resistance reports were identified in the urology department. Based on the local AMR data we suggest the first-line antibiotic recommendations when ESKAPE pathogens are suspected. The directions of the near future antibiotic stewardship program focus on revising the clinical protocols of diagnosis and treatment in each department, increasing the bacteriological samples collection, improving the microbiological diagnostic techniques for AMR identification, and intensifying the epidemiological actions of surveillance, control, and education.

Keywords: ESKAPE; COVID-19; antimicrobial resistance; multidrug resistant organisms; antibiotic stewardship

INTRODUCTION

The World Health Organization (WHO) considers antimicrobial resistance (AMR) among the top 10 priorities for global public health. This phenomenon has developed and spread due to the selection pressure resulting from the excessive or incorrect use of antibiotics [1]. The number of deaths caused by antimicrobial resistance (AMR) could exceed 10 million annually by the year 2050 without active measures promoting the prudent use of antibiotics, improving hand hygiene in hospitals and environmental healthcare hygiene, as well as enhancing food biosecurity [2].

The emergence of multidrug-resistant (MDR) bacteria poses a concerning issue for public health due to the increased risk of healthcare-associated infections and limited treatment options. "ESKAPE" is an acronym for six bacteria of major interest in AMR surveillance systems, namely: (E) Enterococcus faecium, (S) Staphylococcus aureus, (K) Klebsiella pneumoniae, (A) Acinetobacter baumannii, (P) Pseudomonas aeruginosa, and (E) Enterobacter species [3, 4].

The "ESKAPE" pathogens are frequently implicated in severe infections, ranking high among the causes of morbidity and mortality worldwide. However, the WHO has developed a list of priorities within this group. Gram-negative bacilli are considered "critical": carbapenem-resistant CBR Acinetobacter baumannii (A. baumannii), CBR Pseudomonas aeruginosa (P. aeruginosa), third-generation cephalosporin-resistant

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(C3R) Klebsiella pneumoniae (K. pneumoniae), and C3R Enterobacter spp. In the second line of priority are Gram-positive cocci, namely vancomycin-resistant (VAN-R) Enterococcus faecium (E. faecium) and Methicillin-Resistant Staphylococcus aureus (MRSA) [5,6].

Antibiotics are frequently used to treat COVID-19-related bacterial infections. The excessive use of antibiotics during the COVID-19 pandemic can accelerate the emergence and spread of antibiotic-resistant bacteria [7].

In the first year of the COVID-19 pandemic, although many E.U. countries experienced a general decrease in antibiotic consumption both in the community and in healthcare facilities, certain antibiotics, such as azithromycin and ceftriaxone, saw an increase in usage. The reduction in prescriptions was induced by isolation, decreased mobility, and a decline in elective surgical interventions, but the impact of reduced antibiotic use on AMR, especially concerning the ESKAPE group, is insufficiently understood. In a survey conducted in 26 E.U. countries, monitoring antibiotic prescribing behaviors in healthcare facilities was halted in 9 countries, and antibiotic prescriber education programs were interrupted in 11 countries [8,9]. Understanding the link between COVID-19 and antibiotic use can contribute to the development of strategies to limit the impact of infections on vulnerable populations, thereby aiding the global effort to combat infectious diseases.

The study aims to assess the frequency of ESKAPE pathogens and their antimicrobial resistance profile during the COVID-19 pandemic (2020-2022) in a multidisciplinary Romanian hospital.

MATERIALS AND METHODS

A retrospective analysis of the isolated bacterial strains was conducted in the Microbiology Laboratory of the Emergency Military Hospital " Dr. Aristide Serfioti" Galati, derived from various biological samples obtained from hospitalized patients. The hospital is found in the Southeast region of Romania, on the eastern border of the European Union, and includes surgical departments (75 beds), medical departments (100 beds), and an intensive care unit (15 beds).

Escherichia coli and microorganisms in the ESKAPE group had their antibiotic susceptibility evaluated. Escherichia coli was included in the analysis due to its frequent association with horizontal gene transfer of resistance genes from other Enterobacterales, potentially reflecting the resistance profile of Klebsiella pneumoniae or Enterobacter spp, both of which are part of the ESKAPE pathogens [10].

The study was conducted from January 1, 2020, to December 31, 2022. This timeframe coincides with the hospital's focus on COVID-19 support, meaning that the hospital provided healthcare to COVID-19 patients, along with healthcare assistance to the general population, mostly in emergencies.

Microbiological Bacterial Identification Procedures

According to the current work procedures, bacterial isolation was performed by inoculating biological samples either "in sector" or "by exhaustion" on solid media, including Columbia blood agar, Chapman agar, and MacConkey agar (GRASO Biotech, Oxoid - Thermo Scientific, USA), followed by incubation for 24-48 hours at a temperature of 37°C. Biochemical identification of isolated bacterial strains was done through multi-testing and the automatic Vitek 2 Compact method (bioMérieux-l'Etoile).

Antibiotic Susceptibility Testing

Antibiotic susceptibility testing was conducted using either the classic disk diffusion method or the minimum inhibitory concentration (MIC) method with the Vitek 2 Compact automated system, adhering to the current CLSI standards of the working period. The choice of the MIC testing method was contingent upon laboratory availability, the clinical severity of the patient, and the need for an urgent result, particularly in cases of multidrug-resistant bacteria or discrepancies found in the disk diffusion testing.

Depending on the isolated bacteria and the type of sample, specific sets of antibiotics were used for the antibiotic susceptibility testing, including Penicillin's (P – Penicillin - 10 U, A – Ampicillin - 10µg), β-lactam combination agents (AMC – Amoxicillin-clavulanate - 20/10, TZP – Piperacillin-tazobactam - 100/10 µg), cephems (CXM – Cefuroxime - 30 µg; FOX – Cefoxitin - 30 µg, CTX – Cefotaxime - 30 µg, CAZ – Ceftazidime, FEP – Cefepime - 30 µg), monobactams (AZM – Aztreonam - 30 µg), carbapenems (IMP – Imipenem - 10 µg, MEM – Meropenem - 10 µg, ERT – Ertapenem - 10 µg), fluoroquinolones (CIP – Ciprofloxacin - 5µg), macrolides (E – Erythromycin - 15 µg), TE – Tetracycline - 30 µg, lincosamides (DA – Clindamicyn); ansamycins (RIF – Rifampicine - 5 µg), sulfamides (SXT – Trimethoprim/suphamethoxazole - 25 µg), nitrofurans (NF – Nitrofurantoin - 300µg), aminoglycoside (CN – Gentamicin - 10 µg), glycopeptides (VAN – Vancomycin - 30µg, TEI – Teicoplanine - 30µg) and oxazolidinones (LNZ – Linezolid - 30 µg). The disk diffusion testing method used Oxoid Antimicrobial Susceptibility Disks from Thermo Scientific, USA, and Mast Group Ltd from the U.K. BioMérieux-l'Etoile products were employed for minimum inhibitory concentration (MIC) testing, defined as the lowest antibiotic concentration (µg/mL) that inhibits the bacterial growth. Only acquired antimicrobial resistance was taken into consideration, excluding intrinsic resistance. Results of susceptibility for each antibiotic were expressed as resistant, intermediate, or sensitive, and interpretation was made by the Clinical and Laboratory Standards Institute (CLSI) for the respective testing year [11,12,13]. Quality control procedures incorporated the use of reference strains for both identification and antibiotic resistance testing, including Staphylococcus aureus ATCC 29213, ATCC 25923; E. coli ATCC 25922; Pseudomonas aeruginosa ATCC 27853, Enterococcus casseliflavus ATCC 700327, Enterobacter hormaechei ATCC 700323, and Stenotrophomonas maltophilia ATCC 176666.

Data Collection, Interpretation, and Statistical Analysis

After removing duplicates, the antibiotic susceptibility test results were input into the electronic database of the laboratory. Analysis

of the antibiotic susceptibility profile facilitated the identification of significant resistance issues and risks posed by healthcare-associated infections in the hospital. Microorganisms that have minimum inhibitory concentrations (MIC) above the standard cut-off levels are resistant to antibiotics. According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST), a microorganism classified as sensitive (S) indicates therapeutic success with standard antibiotic doses, intermediate (I) responds to therapy after exposure to higher antibiotic concentrations, and resistant (R) exhibits therapeutic failure even after elevated antibiotic concentrations [14].

Multidrug resistance (MDR) was considered if non-susceptibility was found to be at least one antibiotic from two or more classes while maintaining susceptibility to at least one antibiotic from three or more categories15. Other patterns of AMR were also notified: extended-spectrum beta-lactamases (ESBL) in Enterobacterales, carbapenem resistance (CBR) in P. aeruginosa and A. baumannii, methicillin resistance in S. aureus (MRSA) and vancomycin resistance of enterococci (Van-R) [16,17,18].

Statistical analysis of the data used version 19 of the Statistical Package for Social Sciences (SPSS). Descriptive statistics tests were applied to determine frequency, incidence, and prevalence. The $\chi 2$ test was used for comparing categorical variables, considering a significance level of $p<0.01$.

RESULTS

Microbial Profile of the Isolates from Hospital

The microbiology laboratory obtained 1117 bacterial isolates, during the pandemic 2020-2022. The lowest annual frequency of positive cultures was recorded in 2020 (266 strains), when the specific activity of the hospital's departments was most restricted. The average length of hospitalization per year varied over the three years, ranging between 4.32 and 4.96 days.

Table 1: Distribution of the Bacterial Isolates in the Hospital's Departments

Hospital Department		Other surgery	ERT	General Surgery	Urology	ICU	Internal Medicine	Neurology	Pneumo	Other Medical	Total
GPC	*Enterococcus faecium*	-	-	-	1	3	1	1	-	-	6
	Non-faecium	1	1	5	65	12	6	7	3	1	102
	Staphylococcus aureus	1	39	18	3	20	2	2	3	3	91
	Co-Negative	-	-	2	13	13	3	5	1	-	37
	Partial sum	***1***	***40***	***25***	***82***	***48***	***12***	***15***	***7***	***2***	***236***
NF-GNR	*Pseudomonas aeruginosa*	1	18	2	20	18	1	-	7	4	71
	putida	-	-	-	1	-	-	-	-	-	1
	Acinetobacter baumanii	-	-	-	1	1	-	-	2	-	4
	Partial Sum	***2***	***18***	***2***	***22***	***19***	***1***		***9***	***4***	***76***
GNR	*Klebsiella Pneumoniae*	-	8	2	71	27	13	13	13	8	155
	Others	-	6	1	8	1	4	2	4	1	27
	Enterobacter spp	1	6	3	19	5	5	-	4	5	48
	E. coli	1	5	22	179	28	99	82	8	55	479
	Proteus spp	1	10	-	36	4	4	-	-	3	60
	Morganella spp	-	-	1	8	-	1	1	-	-	11
	Citrobacter spp	-	1	2	3	2	2	1	1	1	12
	Serratia marscenscens	-	1	1	4	1	-	1	-	-	8
	Providencia stuartii	-	-	1	1		-	-	1	-	3
	Hafnia alvei	-	-	-	-	1	-	-	-	-	1
	Salmonella spp	-	-	-	-		1	-	-	-	1
	Partial sum	***3***	***37***	***34***	***329***	***69***	***129***	***100***	***31***	***73***	***805***
Total		***6***	***95***	***61***	***433***	***136***	***142***	***115***	***47***	***79***	***1117***

The isolated bacteria were grouped into Gram-positive cocci (GPC), Gram-negative bacilli from the Enterobacterales order, and Gram-negative non-fermentative rods (NF-GNR). The highest frequency of GPC was recorded during the first pandemic year, 25.5% compared to 17% in 2021 and 21.1% in 2022, while NF-GNR was identified more frequently in the second pandemic year, representing 9.1% compared to 6% in 2020 and 5.6% in 2022.

Urine cultures were the most requested microbiological investigations, constituting 80% of bacterial cultures. Much fewer analyses were performed on other biological samples such as 5% purulent secretions, 5% respiratory secretions, 3% ear secretions, and 1% nasal and pharyngeal exudates. Blood cultures represented only 0.45% of the tested biological samples.

The urology department reported the highest number of isolates, representing 38.76% of the total bacterial strains. The Internal

Medicine department accounts for 12.71%, the Intensive Care Unit for 12.17%, and Neurology for 10.29%. Bacterial strains were obtained from between 4.9% and 2.68% of the identified isolates from the ENT, Pneumology, Rheumatology, Surgery, and Cardiology departments. Each other hospital's departments were associated with <1% of bacterial isolates (Table 1).

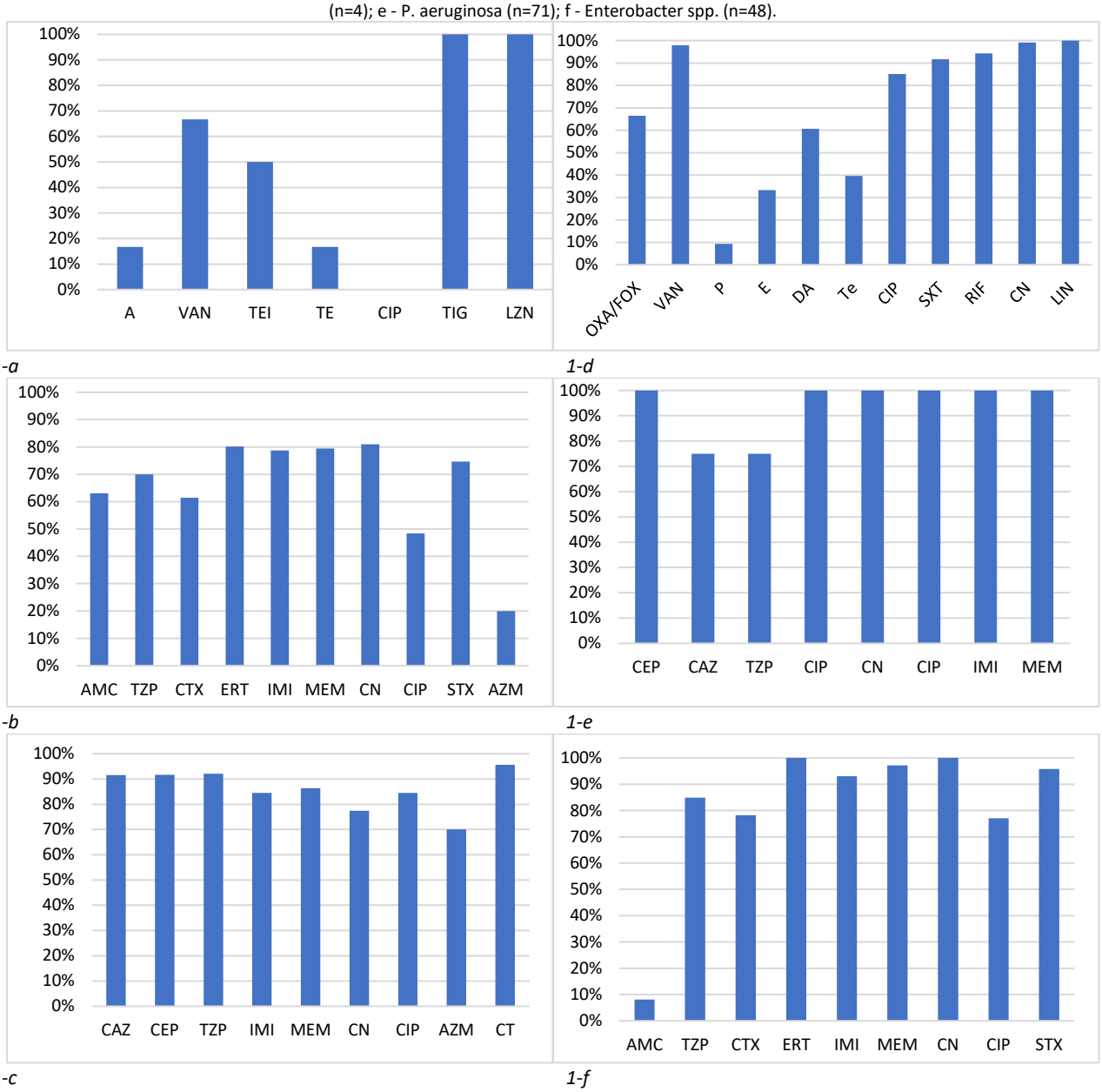
E. coli was isolated with the highest frequency, of 42.8% of species, potentially influencing antibiotic resistance in other Enterobacterales. At the same time, ESKAPE pathogens account for 33.5% of the bacterial strains.

Antimicrobial Resistance Profile of the ESKAPE Pathogens

Enterococcus spp.

Enterococci were identified in 108 isolates with the following distribution: 50.9% E. faecalis, 6% E. faecium, and 43% unspecified Enterococcus spp. E. faecium strains were notified in 6 cases, obtained from the urine cultures (3/6), blood cultures (2/6), and sputum (1/6), mostly on men (4/6), from the ICU (3/6). Each department of pulmonology, internal medicine, and urology reported a single strain. Among the six strains of E. faecium, one-third (2/6) were resistant to Vancomycin and Teicoplanin, and half of the strains (3/6) were multidrug-resistant (MDR). None of the strains were sensitive to Ciprofloxacin (Figure 1a).

Figure 1: Antibiotic susceptibility Profile of the ESKAPE group: a - E. faecium (n=6); b - S. aureus (n=128); c - K. Pneumoniae (n=155); d - A. baumannii (n=4); e - P. aeruginosa (n=71); f - Enterobacter spp. (n=48).



Legend: P–penicillin; A–ampicillin; AMC-amoxicillin-clavulanate; TZP–piperacillin-tazobactam; CXM – cefuroxime; FOX – cefoxitin; CTX- cefotaxime; CAZ-ceftazidime; CEP-cefepime; CT: colistin; AZM-aztreonam; IMP-imipenem; MEM-meropenem; ERT-ertapenem; CIP- ciprofloxacin; E-erythromycin; TE-tetracycline; TIG- tigecycline; DA-clindamicyn; RIF-rifampicine; SXT– trimethoprim/suphamethoxazole; CN-gentamicin; VAN- vancomycin; TEI- teicoplanin; LNZ-linezolid.

Staphylococcus aureus

A total of 128 staphylococcal strains were isolated and identified as follows: 71% S. aureus and 29% Coagulase-Negative Staphylococcus (Co-NS), represented by S. epidermidis (23), S. warneri (4), S. haemolyticus (3), S. hominis (2), S. lugdunesis (1), S. saprophyticus (1), and unspecified Co-NS (3). Most S. aureus strains were identified in nasal or pharyngeal exudates (29.7%), purulent secretions (18.7%), and ear secretions (17.6%). Most samples were taken from patients in the Otorhinolaryngology (ENT) department, Intensive Care Unit, and Surgery departments (85.7%). The frequency of MRSA strains was 33.6%. The MDR rate for S. aureus was 44.5%. The lowest susceptibility of S. aureus was recorded for Penicillin at 9.4%, Erythromycin at 30%, Daptomycin at 60.1%, and Tetracycline at 39.6%. Susceptibility remained at 85% for CIP, 91.66% for SXT, 94.2% for RIF, and 99% for CN (Figure 1b).

Klebsiella pneumoniae

A total of 182 Klebsiella spp strains were isolated, including 85.16% K. pneumoniae, 5.5% K. oxytoca, and 9.3% unspecified species. Most of the cases (64.55%) were found in male patients, and most of the strains came from urine cultures (69%), sputum (9%), and purulent secretions (6%), mainly from the urology department (43.4%), intensive care (15.38%), pulmonology (9.3%), and internal medicine (9.3%). The antibiotic susceptibility profile highlighted AMC 69.8%, CTX 64.1%, TZP 75%, CN 80.9%, CIP 48.3%, STX 76.1%. Resistance to Aztreonam was found in 80% of antibiograms, noting that only 25 strains were tested. The resistance rate to carbapenems in K. pneumoniae strains was 21%, while MDR was found in 18.7% of the isolates (Figure 1c). There is no available data on the susceptibility of reserve antibiotics, as colistin, Ceftazidime + Avibactam. Meropenem + Vaborbactam.

Pseudomonas aeruginosa

Pseudomonas strains were identified in samples taken from 72 patients, of which 71 were P. aeruginosa and one was P. putida. 60.56% of the patients were males. The main products from which P. aeruginosa was isolated included urine (30.55%), ear secretion (23.6%), purulent secretions (15.27%), and sputum (6.9%), mainly from urology, ENT department, and intensive care units. The CBR rate is 15.5%, and the MDR rate is 6.8%. Among the 50 strains tested, resistance to Aztreonam (AZM) was 30%. Resistance issues were also identified for CN 22.5%, CIP 15.5%, but susceptibility was maintained for CAZ 91.55%, CEP 91.66%, TZP 92.1%, and CT 95.56% (Figure 1 e).

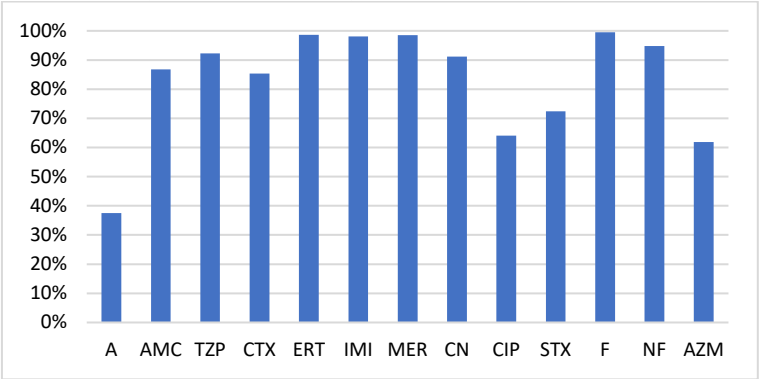
Enterobacter spp

Forty-eight strains of Enterobacter spp were isolated (identified) and distributed as follows: 16.66% E. aerogenes, 50% E. cloacae, and 33.33% unspecified strains. Most strains were isolated from male patients (34/48), in urine cultures (25/48), sputum (7/48), wound swabs (6/48), and pus (5/48). They originated predominantly from the urology department (39.85%), ENT department (12.5%), ICU (10.41%), internal medicine (10.41%), pneumology (8.33%), surgery (3/48), and cardiology (2/48). Isolates were also found in the orthopedics, rheumatology, and diabetology departments. ESBL frequency was found to be 14.58% among isolates, and CBR was identified in 2.85% of strains and MDR in 4.16%. The most concerning antibiotic resistance issues were observed with beta-lactams, influencing the following susceptibility profiles: AMC 8.1%, CTX 78.2%, TZP 84.85%, CIP 77%, SMX 95.75%, CN 100% (Figure 1f).

Antimicrobial Resistance Profile of E. coli

A total of 479 strains of E. coli were isolated, with 61.8% from female patients and 89.5% originating from urine cultures. E. coli strains were obtained from the following departments: urology 37.3%, internal medicine 20.6%, neurology 17.1%, ICU 5.8%, surgery 4.5%, and 14.7% from other departments. Identified antimicrobial resistance issues had frequencies of 15% MDR, 2.6% CBR, and 7.5% ESBL. The lowest susceptibility was found for AMP (37.5%), AZM (62%), CIP (64%), and SXT (72.4%). Better susceptibility was reported for AMC (86.7%), CTX (85.4%), TZP (95.5%), and CN (91.4%). Fosfomycin and Nitrofurantoin testing was limited to the E. coli strains isolated from urine culture, which proved to be susceptible in 100% and 98.25%, respectively (Figure 2).

Figure 2: Antibiotic Susceptibility Profile of E. coli (N=479)



Legend: A – Ampicillin; AMC – amoxicillin-clavulanate; TZP – piperacillin-tazobactam; CXM – cefuroxime; CTX – cefotaxime; AZM – aztreonam; IMP – Imipenem; MEM – meropenem; ERT – ertapenem; CIP – ciprofloxacin; F – fosfomycine; SXT – trimethoprim/suphamethoxazole; CN – gentamicin.
Resistance of E. coli strains to AMC and CTX correlated with the resistance profile of K. pneumoniae ($\chi 2$ test: $p<0.001$) and Enterobacter spp ($\chi 2$ test: $p<0.001$).

Spread of ESKAPE Pathogen Resistance in Hospital Wards

Antibiotic resistance issues among ESKAPE pathogens have variable frequency and impact, both regarding the microorganisms surveyed and within each word, influenced by the characteristics of specific diseases to each specialty.

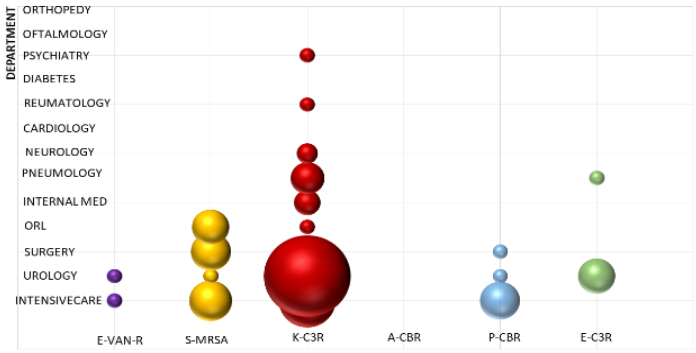
Acinetobacter baumannii is one of the most concerning public health problems worldwide but CBR has not been identified in any of the hospital's departments. All strains highlighted maintained sensitivity to carbapenems and other commonly tested antibiotics, but a single case evidenced an intermediary pattern, signaling decreasing susceptibility that requires vigilant epidemiological surveillance.

Pseudomonas aeruginosa - Carbapenem-resistant cases were found in isolated instances in the ICU, urology, and surgery departments without being considered a source for healthcare-associated infections. The urology department was the primary source for these isolates, but a sporadic case was also reported from the surgery department.

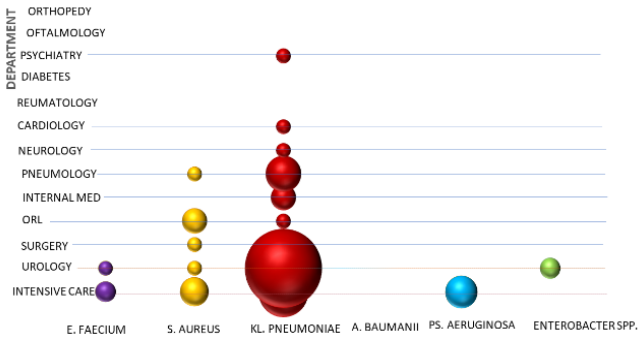
Enterobacter spp - Third-generation cephalosporin-resistant (C3R) was found occasionally, only in the urology department, having the slightest impact among "critical" Gram-negative bacteria on antibiotic stewardship.

The "critical" pathogen Klebsiella pneumoniae C3R is causing the most problems because it was most identified and is spreading the most in hospital wards. It mainly affects the urology department, then the intensive care unit, pneumology, internal medicine, and neurology departments. Epidemiological unrelated cases have also been reported rarely from the ENT, rheumatology, and psychiatry departments (Figure 3 a).

Figure 3: Distribution of ESKAPE Germs in Hospital Departments: a – by Specific AMR; b – by MDR



a: Specific AMR



b. MDR

Among ESKAPE Gram-positive cocci, MRSA draws attention in the intensive care, surgery, and ENT departments, while only a single case was identified in urology. Vancomycin resistance in Enterococcus faecium is reported in isolated cases in the intensive care and urology departments (Figure 3 a).

Total ESKAPE pathogens cumulate specific AMRs (E. faecium Van-R, MRSA, P. aeruginosa CBR, A. baumannii CBR, K. pneumoniae, and Enterobacter spp- C3R) of 30.9%. In addition, MDR is superposing to 21% of these strains. The multidrug resistance of S. aureus, K. pneumoniae, and P. aeruginosa was associated with respect to Methicillin Resistance ($\chi 2$ test: $p < 0.001$), C3R ($\chi 2$ test: $p<0.001$) and CBR ($\chi 2$ test: $p<0.001$). Concerning E. faecium and Enterobacter spp, we found a small number of isolated and MDR very few strains, that are not considered epidemiologically significant.

DISCUSSION

The reported bacterial burden is low, with a yearly average of 1.95 bacterial strains per hospital bed. This result could be explained by the hospital's multidisciplinary profile, mainly in short hospitalization, for patients from the community. The reorganization of COVID-19 support wards has disturbed the specific activities of specialized departments. Additionally, in COVID-19 wards there were

few recommendations for microbiological investigations and properly sampling bacteriological specimens was frequently difficult.

The major challenges of the COVID-19 pandemic for Antibiotic Stewardship, Infections Prevention, and Control were the increase in the number of critical cases, diminution of vigilance in infection control, short supply of specialized staff resources, and absence of guidelines for COVID-19 diagnostic and treatment at the beginning of the pandemic [1,19,20,21]. Moreover, redistribution of lab resources was required during the pandemic, by prioritizing virologic tests and reducing the bacteriological investigations1,19,20. Apart from these general respects, Romania is considered “in the red zone” of European antimicrobial resistance, since is the country with the second highest consumption of antibacterials in Europe and 11% of the population declared antibiotic prescription from the pharmacy, without medical consultation. Therefore, we could assume that patients hospitalized in most wards used antibiotics before hospital admission, so the results of this report should be taken with caution [22,23].

WHO report on antimicrobial resistance (AMR) surveillance in the European Region highlighted a decrease in E. coli isolates in 2020 compared to previous years, attributed to reduced non-COVID-19 care activities and a decline in AMR surveillance vigilance [20,24]. Unlike other countries in the European Region that reported an increase in the frequency of commonly associated healthcare pathogens, such as Acinetobacter baumannii and Enterococcus faecium, these issues were not observed in our study. However, monitoring VAN-R enterococci remains a priority for AMR surveillance in our hospital, given the elevated regional prevalence of Clostridioides difficile infections and the intensive use of oral vancomycin, exerting selective pressure on enteric bacteria [25,26].

Like other European countries, resistance to carbapenems in E. coli and Enterobacter spp. remains low, below 3%, while the rates of C3R in our study exceed 14%, consistent with the European report [1]. The complete susceptibility to Fosfomycin of urinal E. coli isolates justifies the local guideline recommendation of this antibiotic in the initial antibiotic therapy for uncomplicated infections, preserving the β-lactam class [27].

Our study's carbapenem-resistant Pseudomonas aeruginosa (CBR) rate was consistent with the European report (15.5% vs. 17.8%). However, it showed a higher resistance to aminoglycosides (22.5% vs. 9.4%) [1]. Surprisingly, susceptibility to cephalosporins of P. aerugionosa in our setting is above 90%, recommending piperacillin/tazobactam as a first-line therapeutic option for this presuming etiology of infections.

Klebsiella pneumoniae demonstrated the highest frequency among "critical" pathogens but also exhibited the most concerning antibiotic resistance. Resistance rates exceeded 20% for all antibiotic classes, including carbapenems, reaching over 50% for quinolones. It is necessary to systematically the antibiotic testing of K. pneumoniae strains for reserve antibiotics considering colimicin and combinations of ceftolozane–tazobactam, imipenem–cilastatin/relebactam, meropenem–vaborbactam or ceftazidime–avibactam [16]. The recommendation for the first-line treatment of suspected carbapenem-resistant strains should consider these reserve antibiotics. Other additional potent drugs for carbapenem-resistant K. pneumoniae such as plazomicin, eravacycline, cefiderocol or temocillin could become available by governmental regulations [28]. Furthermore, the emergence of K. pneumoniae hypervirulent strains, especially in association with CBR, is linked to antibiotic treatment failure and an elevated mortality rate. Monitoring these variants necessitates using advanced molecular techniques to identify virulence and resistance factors [29].

We have tested the susceptibility on Aztreonam, according to the standardized procedures, although Aztreonam has not been available in Romania for therapeutic use. We found over 30% resistance between the tested Gram-Negative rods, predicting low benefit as a first-choice antibiotic in clinical practice.

Staphylococcus aureus ranks second in the frequency of pathogens with antibiotic resistance risk. The MRSA rate is among the highest in Europe, meaning over 33% of strains. The notably high rate of multidrug-resistant (MDR) strains is mainly attributed to intensive community usage of penicillin, macrolides, and tetracyclines. Vancomycin and Linezolid are valuable options for first-line antibiotic treatment in severe invasive infections, while sulfamethoxazole could be used in non-severe infections. Although not within the study's scope, we observed a higher MDR rate in Coagulase-Negative Staphylococci (Co-N), which colonizes the skin, mucous membranes, and environmental surfaces in the community and the hospital. This may contribute to the transmission of antibiotic resistance to Staphylococcus aureus [30].

ESKAPE pathogens are found in the community, but more frequent in healthcare settings. The mechanisms of antibiotic resistance emergence and persistence of the ESKAPE pathogens are heterogeneous, but they share the ability to build biofilms related to biotic and abiotic surfaces [14]. Regarding the characteristics of our health care services, the source of the ESKAPE pathogens is more probable community than acquired in the hospital but could reflect the regional antimicrobial practices of the practitioners in family medicine and other specialists.

Monitoring and analyzing antimicrobial resistance in the hospital setting is essential for identifying the risks associated with the emergence of "critical" strains and healthcare-associated transmission. Specific resistances within the ESKAPE group, as well as MDR within this group, were more frequently identified in males compared to E. coli, which predominantly originated from females. Both Gram-negative ESKAPE pathogens and E. coli were predominantly associated with urinary tract infections in most cases. This observation could be considered for the risk evaluation in the first-line antibiotic treatment decision, in addition to the predictive clinical scores, such as CarbaSCORE, Tumbarello score, Duke score, or machine learning models [30,31,32,33].

This is the first surveillance report of AMR in the Emergency Military Hospital "Dr. Aristide Serfioti" from Galati, developed to understand the local impact of COVID-19 on bacterial charge, diversity, frequency, and antibiotic resistance, for updating the regional antibiotic stewardship strategy. Revising the clinical protocols for diagnosis and treatment in each department, intensifying the

bacteriological samples collection, and improving the microbiological diagnostic techniques for AMR identification, including high technologies of molecular investigations and point of care antimicrobial resistance tests are highly interests for the near future stewardship. Systematic epidemiological monitoring and control of the hospital environment, hand hygiene procedures stimulation, strict assurance of safe medical procedures, and continuing education are ongoing necessary components of the antibiotic stewardship program.

Limits of the Study

This is a retrospective study, based only on microbiological records. Consequently, the patient history and clinical data were not available. Furthermore, the community or healthcare-acquired source of infection was not analyzed. Hemocultures accounted for only 1% of the total positive samples and 3.18% of them are categorized in ESKAPE group. Therefore, comparing the antimicrobial resistance profile resulting from our study with reference data reported by representative laboratories that monitor antibiotic resistance in epidemiological surveillance networks for invasive bacterial strains, has limited significance [24]. The molecular investigation of antimicrobial resistance mechanisms was not affordable. The antibiotic consumption was not included in the present study but should be correlated with the antimicrobial resistance pattern of the hospital.

CONCLUSION

The COVID-19 pandemic impaired the hospital practice for infections and bacterial diagnostics and weakened the vigilance of antibiotic stewardship. ESKAPE pathogens are almost one-third of the total bacterial isolates, with 21% associated MDR.

The “red flag” for antibiotic stewardship between ESKAPE pathogens is Klebsiella pneumoniae. The directions of the near future antibiotic stewardship program focus on revising the clinical protocols of diagnostic and treatment in each department, to intensify the bacteriological samples collection, to improve the microbiological diagnostic techniques for AMR identification, and to intensify the epidemiological actions of surveillance, control, and education.

Conflicts of interest and sources of funding

The authors declare no conflict of interest. This research received no external funding.

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The current manuscript does not contain previously published materials or self-generated AI text.

Authors’ contribution

Conceptualization, M.A., C-M.V.; methodology, A-V.I, , M.A., C-N.D.; software, I.D., C-S.S; validation, M.A., C-M. V. and A-V-I.; formal analysis, I.D., C-N.D., A.N.; investigation, C-M.V., I.D.; resources, C-M.V. and C-S.S.; data curation, A-V.I.; C-N.D.; writing—original draft preparation, C-M.V., C-S.S, A-V.I., I.D., C-N.D., A.N.; writing—review and editing, M.A.; visualization, C-S.S., A. N.; supervision, M.A.; project administration, C-M.V., A.N. All authors have read and agreed to the published version of the manuscript

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board Institutional Board of Emergency Military Hospital "Dr. Aristide Serfioti" from Galati (RCM 212/M1-544/2023) for studies involving humans.

Patient consent for publication

Not applicable. Our retrospective study used laboratory management which regularly collected data from the databases. The consent for the use of personal data was given by each patient as a routine procedure of the hospital health care provision.

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ORIGINAL ARTICLE

Impact of Physical Performance on Hemodynamic and Cognitive Status in Romanian Older Adults

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Abstract: Background: Frailty is a major challenge for the aging population, increasing the risk of falls, disability, hospitalization, and death. It's common with age, and often linked to reduced physical activity and poor diet, especially in those prone to sarcopenia. Gait speed tests are frequently used to assess mobility in older adults. Materials and methods: This six-month study at "Sfântul Luca" Chronic Disease Hospital involved 143 patients over 65 (mean age 72.85 ± 10.07), 113 of whom were women. The Tensiomed Arteriograph measured heart rate, pulse wave velocity, and central aortic blood pressure to assess acute vascular stiffness. Results: As patients aged, their physical circumstances changed: in the age group 75-84 years ("Very elderly") only 39% of the subjects achieved medium- and good-physical performance, while 56% of them were characterized by low-physical activity (Chi-square test, $p < 0.001$). The mean Mini-Mental State Examination (MMSE) values of individuals with inadequate physical activity were significantly lower (21.02 ± 4.68 points) than those with adequate physical activity (Student t-test, $p < 0.001$). Conclusion: Regular physical activity has been shown to improve hemodynamic factors and potentially slow down arterial aging, thus promoting healthy aging. It is imperative for healthcare professionals to promptly evaluate whether older, frail patients can benefit from rehabilitation, enabling swift recovery through multidisciplinary care.

Keywords: physical performance; hemodynamic status; older adults; cognitive status; personalized rehabilitation program

INTRODUCTION

The clinical state of frailty is one of the most difficult issues facing the senior citizen population. Frailty is linked to a higher risk of falls, disability, hospitalization, and mortality [1] and is thought to be common as people age. The onset of frailty in the elderly is often characterized by muscular weakness, reduced mobility, and constraints in performing routine physical tasks. [2]. Sarcopenia is characterized by the loss of muscle mass and can stem from chronic malnutrition, musculoskeletal changes related to aging, chronic illnesses, micro-inflammation, and related comorbidities. For elderly individuals, being admitted to the hospital is one of the most distressing experiences. The gait speed test is a widely used tool for assessing the mobility of elderly individuals [3]. The level of physical activity and adequate nutrition intake considerably declined among older adults at risk of developing sarcopenia [4]. Muscle weakness and reduced movement speed leading to disabilities characterize sarcopenia, a health condition associated with the aging process among the geriatric population. [5]. Physical activity and gait speed are protective factors for the occurrence of sarcopenia in older adults. The primary physical activity for seniors is walking. Clinical research and clinical objectives are increasingly relying on the evaluation of walking ability [6]. Evaluation of gait speed and its effects on hemodynamic parameters and cognitive status in older persons was the aim of this study.

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MATERIALS AND METHODS

From the 160 patients hospitalized in the months of January-March who met the eligibility criteria: 8 patients refused to participate, 4 patients presented a new diagnosis of oncological disease in the middle of the hospitalization and 5 patients withdrew.

Our study involved 143 patients, 113 of whom were women, and had a mean age of 72.85 ± 10.07 years. This six-month observational, clinical trial was conducted at the Geriatrics Clinic "Carol Davila" in the Chronic Disease Hospital "Sf. Luca." Enrolment was contingent upon the participants fulfilling the subsequent eligibility requirements: being 65 years of age or older; having no self-reported health conditions that would preclude physical examinations; being able to perform basic mobility tasks (such as walking without extreme pain, aching, or stiffness); and not being undergoing cancer treatment, knee or hip replacement, heart or spinal surgery, myocardial infarction within the previous six months, or experiencing chest pain while walking within the previous 30 days. A MMSE score < 20 points resulted in the exclusion of participants. Before participating, each participant gave written, informed consent. The Clock Drawing Test (CDT) is a simple tool used to check for early signs of dementia, scoring up to 10 points. We used the Short Physical Performance Battery (SPPB) to measure physical activity, which includes the tandem standing, 4-meter walk test, and Up-and-Go [7]. For functional capacity, we used the standardized scales Activity Daily Living (ADL) with ranges from 0 to 6 points and Instrumental Activity Daily Living (IADL) with ranges from 0 to 8 points, where a high score indicates high function [8, 9]. We measured hand grip strength using a hydraulic dynamometer and used the Tensiomed Arteriograph to evaluate arterial vascular stiffness: pulse wave velocity (PWVao), heart rate (HR), central aortic systolic blood pressure (SBPao), and central aortic pulse pressure (PPao) [10].

To illustrate the degree of comorbidity, we categorized the patients into three groups based on a comorbidity index: low comorbidity index, which represented patients with up to two chronic pathologies; moderate comorbidity index, which represented patients with three to five chronic pathologies; and high comorbidity index, which represented patients with more than five chronic pathologies.

The inclusion of patients with metabolic syndrome was achieved by evaluating those with 3 criteria (MS3) or with the presence of 4 of them (MS4) and all 5 criteria (MS5). In addition, we conducted a search through reference lists of pertinent publications, Google Scholar, EBSCOhost, and Medline in order to find published hand grip strength norms.

All determinations are performed according to the protocol and the results are analyzed according to standardized scales. This study was approved by the Ethics Commission (9/09.12.2023).

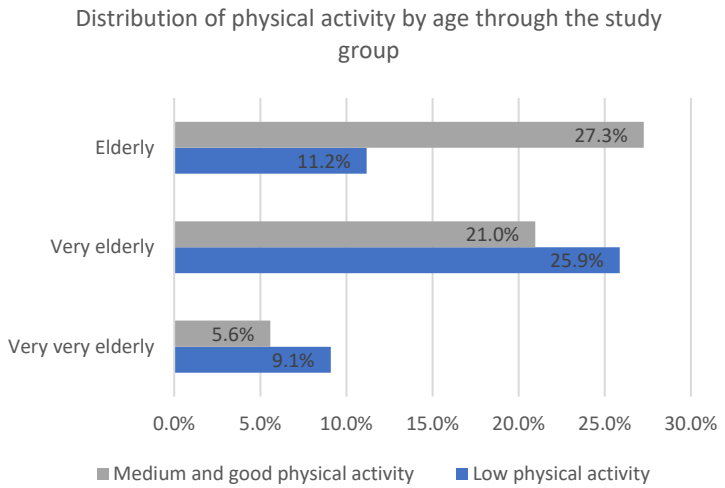
Statistical Analysis

All the data from this study were analyzed using IBM SPSS Statistics 25 and illustrated using Microsoft Office Excel/Word 2021 Stundent's t-test was used for parametric distributions. Qualitative variables were written as absolute frequencies with percentages and were tested between groups using Fisher's Exact Test.

RESULTS

The age caused changes in the physical status of patients. Thus, 56% of the subjects with low physical activity were in the age group 75-84 years, and only 39% of very elderly subjects were characterized by medium and good physical activity (Chi-square test, $p < 0.001$). Also, in the "very, very elderly" age group (over 85 years), we noticed the same statistically significant difference between the two groups (see Figure 1).

Figure 1. Distribution of physical activity by age



Within the group, there is no statistically significant difference in terms of physical performance and the number of associated diseases (expressed by the comorbidity index, student T-test) (see Table 1).

The functional capacity of the elderly in the study group was relatively normal, with no more than two activities affected, especially in the instrumental activities of living: the mean IADL is 6.66 ± 1.71 (out of a maximum of 8 points), and the mean ADL is 5.74 ± 0.92 (out of a maximum of 6 points). Quantitative independent variables were tested between groups using Mann–Whitney U tests (see

Table 2).

Table 1: Physical activity and comorbidity index

Characteristic	Low physical activity (N = 66)	Medium and good physical activity (N= 77)	p
Comorbidity index			
Low	1 (2%)	2 (2%)	0.389
Moderate	52 (79%)	66 (86%)	
High	13 (19%)	9 (12%)	
Metabolic syndrome criteria			
Without MS[1]	18 (27%)	14 (18%)	0.353
MS3	23 (35%)	34 (44%)	
MS4 and MS5	25 (38%)	29 (38%)	
Diabetes			
Yes	29 (44%)	40 (52%)	0.339
No	37 (56%)	37 (48%)	

Table 2: Physical performance and functional capacity in the studied group

Characteristic	Low physical activity (N = 66)	Medium and good physical activity (N = 77)	p
ADL	5.50 ± 0.93	5.95 ± 0.87	0.004
IADL	6.06 ± 1.81	7.17 ± 1.43	< 0.001
Subjective fatigue			
Rare	8 (12%)	17 (22%)	
Sometimes	9 (14%)	37 (48%)	< 0.001
Often	49 (74%)	23 (30%)	
Hand grip strength	11.74 ± 2.9	17.08 ± 4.94	< 0.001
Walking speed	0.34 ± 0.1	0.69 ± 0.13	< 0.001
Statin treatment			
Yes	29 (44%)	39 (51%)	0.423
Not	37 (56%)	38 (49%)	

Physical performance and impact on daily activity scores show a direct relationship between the functionality and the SPPB values. A statistically significant difference was found in IADL scores within the group with low physical activity (6.06 ± 1.81 compared to 7.17 ± 1.43, Student's t-test, $p < 0.001$). Additionally, basic individual needs, such as eating and washing, are impacted in the group with reduced functionality, as measured by the ADL, like those with lower physical performance (Student's t-test, $p = 0.004$) (see Table 2).

Hand grip strength measured by a dynamometer, adjusted for age, gender, and height, revealed a significant difference in the group with low physical activity, with an average strength of just 11.74 ± 2.9 kg (Student's t-test, $p < 0.001$) (see Table 2).

In the context of long-term treatment of elderly patients with chronic cardiovascular disease, statins are often associated with the development of sarcopenia, chronic fatigue, and reduced physical activity. However, our study findings revealed no statistically significant correlation between the use of statins and the decline in hand grip strength or physical performance among the elderly patients in our study group. Remarkably, more than half (51%) of the elderly patients undergoing statin treatment maintained satisfactory levels of physical activity (see Table 2).

In our analysis of walking speed, we calculated patients' movement rates and correlated them with some hemodynamic parameters (HR, PWVao, PP) and functional capacity, through multiple regression analyses. We divided the patients into three groups: the first group (home movement) consisted of elderly individuals at heightened risk of disability who have limited mobility confined to their residence, with a walking speed of up to 0.4 m/s; the second group (limited community movement) included elderly people engage in movement within the community and are at moderate risk of losing their autonomy, with a walking speed between 0.4 - 0.8 m/s; the third group (full mobilization) comprised individuals who are not exposed to the risk of disability and are fully mobile with a walking speed exceeding 0.8 m/s (see Table 3).

The results showed a significant statistical difference on the pulse pressure (PP) ($p = 0.001$). This indicator could potentially serve as a valuable predictor for gauging cardiovascular risk and assessing disability risk, particularly in relation to walking speed.

Regarding the cognitive level there is a clear difference between the two groups. The mean MMSE values, which assess the cognitive status of the subjects, are significantly lower (21.02 ± 4.68 points) among those with low activity compared to those with good physical activity (Student t-test, $p < 0.001$) (see Table 4).

Table 3: Distribution of patients according to walking speed

	Group 1 = home movement (N = 48)	Group 2 = limited community movement (N = 71)	Group 3 = full mobilization (N = 24)	p
ADL	5.46 ± 0.84	5.80 ± 0.95	6.13 ± 0.85	0.011
IADL	6.19 ± 1.8	6.75 ± 1.71	7.33 ± 1.09	0.021
PWVao	10.37 ± 1.74	9.94 ± 1.93	9.95 ± 1.63	0.419
PP	**66.71 ± 14.23**	**65.17 ± 15.31**	**53.42 ± 12.75**	**0.001**
HR	68.81 ± 12.7	66.61 ± 11.36	65.33 ± 7.02	0.404

Table 4: Correlation of hemodynamic and cognitive parameters with walking speed

Characteristic correlation	Coefficient	p
PWVao and SPPB	- 0.141	0.092
HR and SPPB	- 0.166	0.047
Walking speed and SBPao	- 0.149	0.076
Walking speed and Body Mass Index (BMI)	0.125	0.138
Walking speed and MMSE	**0.339**	**< 0.001**
Right-Hand grip strength and SPPB	**0.422**	**< 0.001**
Left-Hand grip strength and SPPB	**0.440**	**< 0.001**
Fatigue and statin treatment	0.064	0.450

The presence of this difference comes as an important finding that supports the potential role of physical exercise in preventing cognitive impairments in the elderly. Given the limited effectiveness of current drug treatments for dementia, geriatric clinicians should place greater emphasis on incorporating physiotherapy programs for these elderly patients.

Another important finding is the difference between the two groups in the case of the Clock Drawing Test (CDT), which is easy to use, quick to administer, and can be implemented as a screening tool in primary care settings [11].

The group of those with low physical activity had an average CDT score of 6.63 ± 1.33 points (out of a max. 10 p), compared to an average score of 7.96 ± 1.72 points among those with good physical performance (Student t-test, $p < 0.001$). Our findings once again emphasize the importance of the age-old adage, "Mens sana in corpore sano".

DISCUSSION

Regular physical activity is not only crucial for maintaining autonomy but also for preserving cognitive function [12]. It is widely recognized that consistent aerobic exercise enhances cardiorespiratory function, reduces arterial stiffness [13], diminishes cardiovascular risk factors, and lowers cardiovascular mortality. Conversely, anaerobic exercises promote skeletal muscle strength and are instrumental in preventing age-related muscle atrophy [14]. Elderly patients can benefit from the high level of education of nurses, which influences the degree of clinical autonomy. The nurse needs to be aware of any barriers to learning, like loss of hearing or decline of vision and should tailor his or her education for that specific patient [15].

Physical activity is an effective strategy for protecting against sarcopenia and promoting healthy aging. Most studies on exercise in elderly people show that participants achieve positive results, although maintaining muscle strength appears to depend on the continued implementation of certain types of physical activities. One of the conclusions from a meta-analysis of 10 studies was that there was no consistency in the measurement of sarcopenia, indicating a need for further investigations [16].

For elderly people, regular exercise (at least one hour, at least twice a week) through personalized exercise programs can have beneficial cardiovascular effects, such as lowering blood pressure, improving skeletal muscle perfusion, and enhancing glucose utilization in myocytes. Additionally, regular exercise helps maintain muscle fiber quantity and supports skeletal muscle strength [17]. Numerous studies have demonstrated the significant impact of this factor on recovery rates in neurological system disorders and cardiovascular diseases, both of which are primary contributors to disability and diminished quality of life (QoL) [18-20].

The QoL significantly influences patients' adherence to treatment and their overall recovery, making it a pivotal endpoint in clinical research. Aspects such as pain management, emotional well-being, social interactions, and independence profoundly impact patient outcomes. Consequently, enhancing QoL becomes a primary objective from the point of diagnosis. While both patients and physicians acknowledge the importance of prolonging survival, maintaining an optimal quality of life throughout the treatment process is equally imperative [21]. We consider that physical activity plays a major role in enhancing QoL. Due to the Coronavirus (COVID-19) pandemic, many elderly individuals—already a high-risk group for severe illness and adverse SARS-CoV-2 outcomes—opted to remain at home out of fear of contracting the virus, regardless of their associated comorbidities. Consequently, it is hypothesized that a significant

number of older adults are now facing the repercussions of that period, notably sarcopenia, which is linked to a lack of physical activity. As a result, these individuals are now tasked with recovering from that phase, underscoring the need to increase awareness about the importance of physical exercise in this population [22]

In our study, the measurement of muscle strength through the dynamometer revealed a significant difference in the group of elderly patients with low physical activity (Student t-test, $p < 0.001$). Traumatic injuries accounted for the largest percentage of rehabilitation cases in Romania (73.17%), with musculoskeletal illnesses coming in second (70.06%). Reduced recovery was observed in cases of neurological system disorders (50.56%) and cardiovascular diseases (44.23%) [18].

Although other studies have debated the potential link between statin administration in the elderly and the development of sarcopenia, fatigue, and decreased physical activity [23], our group did not find a positive correlation supporting this relationship. Hence, it endorses the recommendations for the continued utilization of statins, even in advanced age, as they have exhibited protective advantages in averting cardiovascular incidents.

Analyzing and interpreting walking speed presents a challenge for clinicians, but recent specialist studies have provided new insights into survival and mortality predictors. Normal walking speed requires a relatively low level of energy consumption [24, 25]. Our study found statistically significant results related to pulse pressure (PP), which is considered a predictor for evaluating disability risk in the elderly population [26].

Cognitive status can be improved by exercise. Several prospective studies have demonstrated that maintenance of higher levels of physical fitness helps protect against cognitive deterioration, even at an advanced age [12,27,28]. Conversely, poor physical performance among older adults may accelerate cognitive decline and lead to early onset of dementia [29, 30]. Additionally, muscle strength has been linked to cognitive performance [31,32]. Promising trials utilizing AI and technology, which show significant improvements in autonomy and reduced reliance on human resources point to a bright future for the medical care and recovery of elderly patients with cognitive impairments [33,34,35].

Several limitations of the present study should be acknowledged. First, the study sample was predominantly female, which could potentially influence the results. Second, the study group was relatively small, and there was a lack of homogeneity, which may affect the comparability of the findings with the broader Romanian population.

CONCLUSION

Maintaining physical performance, especially in the elderly with associated chronic diseases, has an important role in maintaining autonomy and quality of life, especially in the very old and very, very old age groups that become frailer. Assessing hand grip strength can provide valuable insights into physical performance and guide lifestyle optimization and treatment recommendations for elderly patients. Exercise training has been shown to improve hemodynamic status (including SBP, PP, SBPao, PPao) and may help delay arterial aging, playing an important role in healthy aging. Muscle strength, balance, flexibility, endurance, and mobility are all aspects of whole-body functioning that are included in physical performance. When older adults perform poorly physically, they experience a decline in their quality of life, a loss of cognitive function, an increase in their risk of falling, poorer clinical outcomes, and a reduction in their independence when it comes to doing activities of daily living (ADL).

Early detection of rehabilitation potential in frail elderly patients is essential for initiating timely recovery interventions through specialized medical services and multidisciplinary teams.

From a practical and clinical perspective, developing a consistent program of adapted, personalized physical activities is necessary. Such programs can positively affect functional parameters and significantly enhance the quality of life for elderly individuals. In order to corroborate these findings and draw further conclusions, it is essential to conduct studies encompassing a more diverse and extensive demographic.

Conflicts of interest and sources of funding

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Authors' contribution

Conceptualization, J.A., S.M.A., A.Z. and C.O.; methodology, R.M., A.P..; software, S.M.G, C.D.G., A.G.P .; validation, J.A., S.M.A., A.Z. and C.O; formal analysis, J.A., A.Z., V.M.A.M., M.N; investigation, V.M.A.M., C.D.G., S.M.G.; resources, A.G.P., S.M.A., M.N., C.O.; data curation, S.M.G, C.D.G, A.G.P., M.N.; writing—original draft preparation, J.A, S.M.A, A.Z., C.O.; writing—review and editing, J.A., S.M.A., C.O.; visualization, A.Z., R.M., S.M.A.; supervision, S.M.A, J.A, C.O.; project administration, A.Z., J.A.; funding acquisition. All authors have read and agreed to the published version of the manuscript

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Commission of the HOSPITAL OF CHRONIC DISEASES "SF. LUCA" (protocol code 9, date of approval 09.12.2023).

Patient consent for publication

Written informed consent to participate in the research was obtained from each patient/subject..

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REVIEW

Case Management of Delirium in Patients with Major Neurocognitive Disorders

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Abstract: Delirium is associated with lower quality of life, increased healthcare costs, longer hospitalizations, and worse prognosis when detected in patients who are already confronted with a severe and invalidating disease, like the major neurocognitive disorder (MND). In order to identify the most evidence-based interventions that could be included in case management for patients with both delirium and MND, this narrative review explored three electronic databases (Pubmed, Cochrane, and Web of Science/Clarivate) for primary and secondary sources dedicated to this topic. All papers published in English between the inception of each database and September 2024 were screened for relevant data on pharmacological and non-pharmacological therapies targeting delirium. The results supported the use of a multicomponent approach as the first line of treatment, mitigating the precipitating factors, and only as a second line, the use of pharmacological instruments. There is a lack of validated therapies targeting specifically the delirium superimposed on MND, most of the recommendations being extrapolated from studies with delirium in the general population or in elderly patients with different organic diseases. Further studies are required to investigate the specifics of delirium in patients with MND and potential strategies focused on neurobiological mechanisms instead of just clinical manifestations.

Keywords: delirium; acute confusional states; dementia; major neurocognitive disorders; cognitive impairment; delirium assessment tools; antipsychotics

INTRODUCTION

Establishing adequate case management strategies for patients diagnosed with delirium is among the most challenging aspects of liaison psychiatry due to the complexity of the interactions between psychiatric phenomenology and organic pathology. Psychiatrists working in general hospitals are frequently called for consultation by colleagues with different medical specialties to „calm down" patients who suddenly become confused and agitated or, on the contrary, to „wake up" patients who abruptly become non-responsive to external stimuli. This psychiatric disorder is, however, far from being possible to approach by a single therapeutic method and requires an individualized case conceptualization and treatment. While in some cases, identification and correction of the causal factor(s) are simple and may be conducted promptly, such as in the case of severe dyselectrolytemia or hypoglycemia, in most cases, extensive investigations and multiple interventions are needed before the symptoms of delirium may be adequately managed. In this context, it would be necessary to mention that delirium is frequently deceptive because it can be the final manifestation of multiple organic comorbid conditions and a superficial investigation and treatment of the patient may make his or her prognosis worse. Therefore, psychiatrists should be aware of the intricate etiopathogenesis of delirium and of the necessity to investigate and treat such patients within a multidisciplinary framework. These considerations become more obvious when patients with severe chronic cognitive deterioration are evaluated since their anamnesis is reputedly difficult and the psychiatric exam also is frequently challenging.

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Due to the changes in the names and definitions of neurocognitive disorders along the main classifications of psychiatric disorders, edited by the World Health Organization (WHO) and American Psychiatric Association (APA) [1-5], a trans-

nosographic analysis is considered necessary to configure the framework of case management in patients affected by these conditions. Although there is a clear tendency to increase the concordance between the APA's Diagnostic and Statistical Manual of Mental Disorders (DSM) and the WHO's International Classification of Diseases (ICD) criteria for the diagnosis of psychiatric disorders, there are still important nosographic differences that need to be acknowledged by clinicians due to practical reasons.

Major neurocognitive disorders (MND) are defined, according to the latest editions of the DSM (DSM-5 and 5 TR, published in 2013 and 2022, respectively), by significant cognitive decline compared to the individual's previous level of performance in at least one cognitive domain; this cognitive impairment has to be supported by concerns reported by the patient, significant caregiver or clinician; also, a substantial deficit in cognitive performance, documented by a quantitative clinical assessment is required [1,2]. Also, significant interference of these cognitive impairments with the individual's ability to perform independent daily tasks is needed for the diagnosis, and the exclusion of other mental disorders is required as a differential diagnosis in these cases [2]. It is important not to consider the diagnosis of MND in patients who present cognitive impairment exclusively during the periods of delirium [2]. Once the diagnosis of MND is made, the presumed type of disease must be formulated, and the specifiers „with/without behavioral disturbance" and „severity" (mild/moderate/severe) are added [2].

The previous edition, DSM IV-TR, not only used different terminology for MNDs, which were called „dementias", but also the diagnosis criteria included neurological signs, i.e., aphasia, apraxia, agnosia, and the existence of disturbances in executive functioning, besides the memory impairment [3]. Regarding the ICD-10 and ICD-11, their perspective on the terminology is quite similar, and the term „dementia" is preserved in both editions, but in the latest version of ICD, there is an increased focus on the behavioral or psychological disturbances in dementia (BPDD), which received their own set of codes [5].

According to DSM-5 and 5 TR, to formulate a diagnosis of delirium, the clinician should confirm the existence of a disturbance in attention and awareness, accompanied by disturbances in cognition, i.e., memory, orientation, language, visuospatial abilities, or perception [1,2]. Additionally, this diagnosis requires an abrupt onset (e.g., hours to a few days), a change from the baseline level of attention/awareness, and a tendency towards fluctuation in severity during a single day [1,2]. The clinician must exclude the presence of a preexisting or evolving neurocognitive disorder and the presence of a coma or related conditions [1,2]. DSM-5 and 5 TR also state, as an essential criterion, the evidence supporting the direct causal-ship between a general medical condition, substance withdrawal/intoxication, exposure to a toxin/medication, or multiple etiologies and the symptomatology of delirium [1,2]. There are several specifiers for delirium, i.e., those related to the etiology, specifiers of severity (acute/persistent), and level of behavioral symptoms (hyperactive/hypoactive/mixed level of activity) [1,2].

When comparing the diagnostic criteria for delirium in the DSM-IV TR, DSM-5, and DSM-5 TR, several differences emerge [1-3]. The latest editions emphasize the need for disturbances in attention and awareness to represent a change from baseline, exclude coma from the category of delirium, and recognize the potential for multiple cognitive domains to be impaired by this disorder. Furthermore, both DSM-5 and DSM-5 TR provides a more comprehensive list of etiological types of delirium than does the DSM-IV TR [1-3].

The WHO's ICD-10 (the 2019 version) specifies that delirium is „an etiologically non-specific organic cerebral syndrome" that is characterized by disturbances of consciousness and attention, perception, thinking processes, psychomotor behavior, emotions, and the sleep-wake rhythm [4]. ICD-10 mentions that the duration of delirium is variable and the degree of severity may be different, from mild to severe [4]. Regarding the possible etiological considerations, ICD-10 includes different codes for delirium not induced by psychoactive substances, in cases where it is not superimposed on dementia, in cases of delirium superimposed on dementia, and contains codes for other types of delirium (e.g., mixed delirium, or post-surgery), and delirium-unspecified; delirium is also a complication of various withdrawal/intoxication states or somatic diseases (e.g., thyroid storm, kidney failure) [4].

The latest edition of the WHO Classification of Diseases (ICD-11) expands the definition of delirium (but preserves the core dimensions-phenomenological description, changes in functionality) and specifies the main differential diagnoses and potential etiologies, i.e., direct physiological effects of a medical condition, direct physiological effects of a substance or medication (including withdrawal), and unknown factors [5]. Residual categories, such as multiple etiological factors and other specific causes, are also coded [5].

The phenomenon of delirium in patients diagnosed with MND is very complex since the relationship between the two pathologies is far from being easy to define in each case. Individuals with MND have an increased risk of delirium onset when compared to the general population, but delirium in itself represents an independent risk factor for developing MND [6]. Also, delirium may be more difficult to diagnose in patients with MND because disentangling cognitive changes and sensorium clouding in a patient with an already deteriorated cognitive status, based on clinical evaluation, is challenging. Even more, confusional episodes appearing in patients with MND can worsen the cognitive decline and the overall functioning level [6]. It must also be mentioned that MNDs associate multiple well-defined psychiatric disorders (e.g., mood, anxiety, psychotic) as well as BPDDs, which creates supplementary difficulties in detecting new-onset cognitive decline due to delirium [7]. These convoluted interactions between delirium and MND are represented in Fig.1., but caution is recommended when interpreting these relationships due to the intricacy of organic and psychological factors (e.g., infectious diseases may trigger delirium, and delirium may, in patients with MND, worsen the psychological long-term evolution, or, a psychological trigger may be responsible for the clouding of sensorium in a patient with MND, which also may worsen the long-term biological evolution of the patient, if the trigger is not properly identified and corrected; also, psychosocial factors may inadvertently worsen a somatic disease that, in turn, may aggravate the preexisting MND).

Figure 1: The interaction between delirium and major neurocognitive disorders

Organic conditions associated with MND, ie., PD, AD, CJD
Triggers for delirium (OTand/or PT)
MND
Delirium
Worsen MND prognosis and life expectancy, duration of hospitalisation, healthcare costs

AD= Alzheimer's disease; CJD= Creutzfeldt-Jakob disease; MND= major neurocognitive disorder; OT= organic triggers; PT= psychological triggers; PD= Parkinson's disease

Although the phenomenology of delirium encompasses prodromal and subsyndromal stages [8], no consensus about corresponding specific symptoms exists, making it difficult for clinicians to identify such forms of delirium in daily practice. Due to the complexity of the phenomenological presentation of delirium, the differential diagnosis is another important challenge for clinicians [8]. More exactly, delirium consists of core manifestations, which are expected to be present in all cases (e.g., awareness alterations), frequently met symptoms (e.g., motor activity dysfunctions), and associated, variable symptoms (e.g., hallucinations), which may reflect the etiological medical or toxic factors [8]. The evolution of delirium is difficult to predict because it is dependent on etiological factors, but it was reported that almost 57% of hospitalized patients may still have delirium after discharge from the hospital [9].

The reported prevalence in hospitalized patients varies across studies, depending on the criteria used, the type of department reporting the cases, the instruments applied for quantifying the severity of the symptoms, etc. The prevalence of delirium was reported between 1 and 31%, and the incidence between 3 and 25% [10-12]. For example, 39% of the patients admitted to intensive care units (ICUs) were diagnosed with delirium, according to a cross-sectional multicenter study (N=256 participants) that used a screening checklist as the core methodology of assessment [13]. In hospitalized patients aged ≥65, delirium was reported in the case of 55.4% of the 327 participants using the 3-Minute Diagnostic Confusion Assessment Method (3D-CAM) [9]. A surprisingly high rate of patients with delirium (35.4%) were not identified by the treating team, indicating the need for increased awareness about the existence of this neurocognitive disorder [9]. Also, it is important to explore the possibility of multiple etiologies in patients with delirium, including organic acute diseases, chronic illnesses that are acutely decompensated, new drugs recently introduced for the treatment of a physical or mental disorder, different environmental stressors, etc. [14-16].

The presence of delirium was independently associated with worse clinical prediction of survival, lower quality of life, and increased healthcare costs through longer hospitalizations have been reported in patients with delirium [17-19]. More specifically, an economic analysis of healthcare for older hospitalized patients with or without Alzheimer's disease and related dementias associated with delirium showed that in the first group, the adjusted mean difference in costs related to delirium was almost 35000 USD, and these costs increased progressively over one year vs. non-MND patients [20]. The same study revealed that patients with Alzheimer's disease-related MND were more likely to develop delirium (51% vs. 24%) and die within one year (38% vs. 21%), all values being statistically significant [20]. Because delirium is considered a modifiable factor for prognosis in patients with MND and, frequently, a preventable one, the necessity for a correct diagnosis and early treatment, whenever delirium is identified, could have both short-term and long-term substantial benefits for the MND population. According to a systematic review, the prevalence of delirium superimposed on dementia varies between 22% and 89% in hospitalized patients aged over 65 [21]. Such high prevalence indicates, once again, that there is an acute need to detect and treat delirium actively in vulnerable populations.

This narrative review aims to identify the most valid interventions that could be included in case management for patients with delirium associated with MND. Because it was anticipated that the sources for this specific population might be scarce, the secondary objective included finding case management recommendations for patients with delirium in clinical populations, regardless of the organic or psychiatric background; these supplementary data were explored to see if they allow for being extrapolated to MND + delirium cases.

MATERIALS AND METHODS

This review explored three electronic databases (Pubmed, Cochrane, and Web of Science/Clarivate) for primary and secondary sources dedicated to this topic, using as keywords „delirium", OR „confusional episodes" OR „confusion superimposed on dementia"

AND „major neurocognitive disorder" OR „dementia" AND „pharmacologic*" OR „drug" OR „non-pharmacologic*" OR „psychosocial". All papers published in English between the inception of each database and September 2024 were screened for relevant data on pharmacological and non-pharmacological therapies targeting delirium. The results were grouped into two classes: (1) guidelines for patients with delirium in clinical populations and (2) case management for patients with delirium and neurocognitive disorders.

RESULTS

Based on the 36 sources reviewed in the first section, dedicated to delirium case management in clinical populations, and 15 sources (partially overlapping) focused on the evaluation and treatment of delirium superimposed on MND, the following results are presented.

Recommendations for case management in patients with delirium in the hospital settings

The papers reviewed and grouped in this section were distributed according to their main clinical use, i.e., (1) validated tools for screening and monitoring delirium and (2) therapeutic recommendations, since these two components were considered essential for clinicians to construct a case management plan (Fig.2).

Instruments for detection of delirium and its severity quantification in clinical population

There are many instruments for the diagnosis and monitoring of the presence of delirium, some of them being more widely used and largely validated than others. CAM was developed by an expert panel through a consensus process and has the clear advantage of its brevity and easiness of administration [22]. CAM may be applied in less than five minutes and consists of nine criteria derived from DSM III R, the main symptoms of delirium being acute onset and fluctuating course, lack of attention, disorganized thinking, and altered sensorium [22]. Different versions of this instrument emerged, such as CAM-ICU, which is dedicated to patients admitted to intensive care units and can be administered by non-specialists [23].

4-AT is another tool conceived for the screening of delirium symptoms in elderly patients and demonstrated good sensitivity and specificity for hospitalized subjects [24]. This instrument has four items, i.e., alertness, two items for cognitive function, and one for fluctuation in mental status [24].

The NEECHAM (Neelon and Champagne) Confusion Scale is also used for rapid assessment of delirium and has been proven to have good internal consistency and interrater reliability, and it also correlated well with the Mini-Mental State Examination [25]. This tool has nine scale items, is easy to use, and can be scored by nurses with minimal training. Also, NEECHAM may be administered initially and periodically to monitor mental status [25].

The Observational Scale of Level of Arousal (OSLA) can be used for the identification of abnormal levels of arousal associated with delirium and may be administered for screening and monitoring purposes [26]. The items refer to eye-opening, eye contact, posture, and movement, and the total score is between 0 and 15 [26].

Therapeutic and prophylactic recommendations in patients with delirium

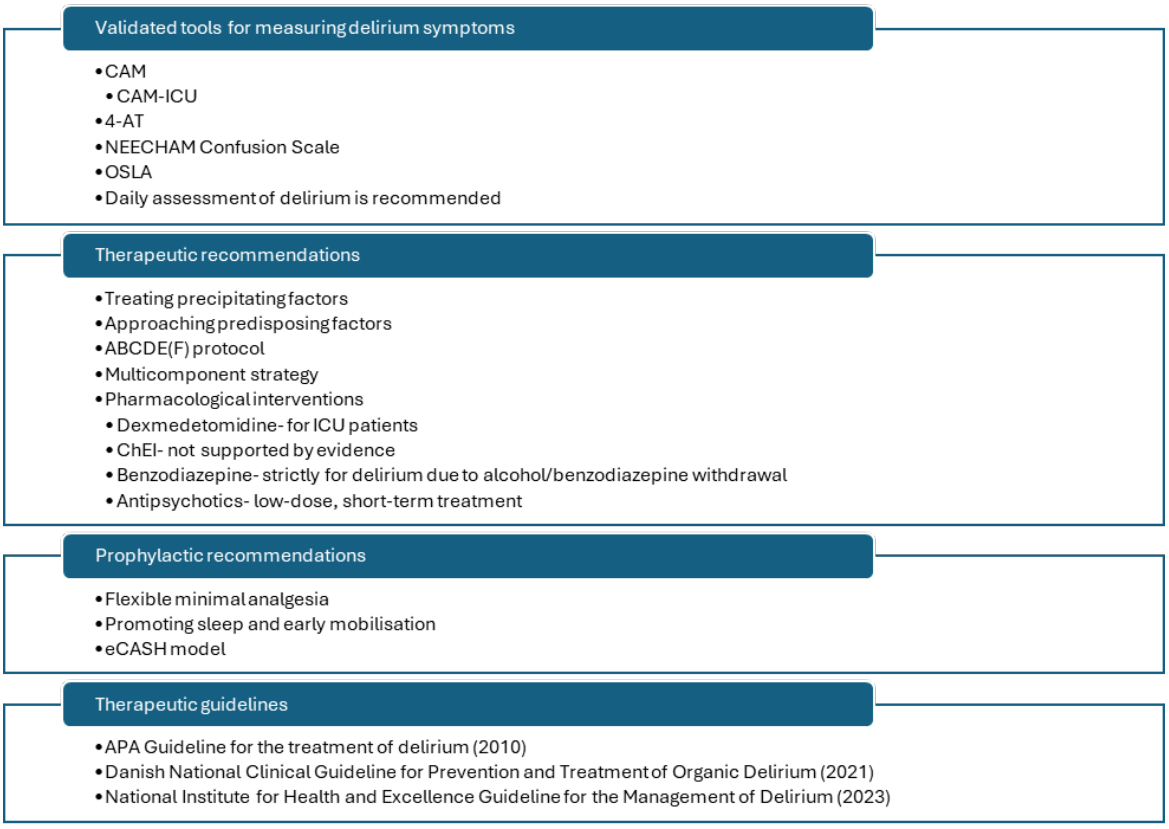
Regarding the therapeutic approaches to delirium, after the diagnosis of an acute confusional state was formulated, the first step is to analyze the potential contributors to the onset of this disorder. Predisposing and precipitating factors must be evaluated, and modifiable etiological factors should be addressed [27]. The case management of patients with delirium has as the main objective the correction of the biological disequilibrium that fueled the confusional state, but the prevention of relapse is also of major interest since several causes may be chronic or recurrent. According to an expert consensus on delirium management, „early identification and intervention of subclinical delirium can reduce the risk of clinical delirium" [28]. Also, daily assessment of at-risk patients is important for early detection of delirium and adequate therapeutic interventions [28].

The most common precipitating factors that should be approached during the evaluation of a patient with delirium are infections, electrolyte imbalances, drugs (medications, drugs of abuse-intoxication/withdrawal, toxic substances), pain, organ failures, traumas, metabolic and nutritional imbalances, central nervous system (CNS) pathologies, environmental factors (e.g., sensorial deficits for patients with neurocognitive disorders, immobilization, sleep-wake cycle dysfunctions), but also psychiatric factors (e.g., anxiety, insomnia or depression in elderly patients with severe organic disease).

The ABCDE/ABCDEF protocol was suggested for managing delirium [29,30]. This acronym stands for (a) assessing, preventing, and managing pain, (b) both Spontaneous Awakening Trials and Spontaneous Breathing Trials (SAT and SBT, respectively), (c) choice of analgesia and sedation, (d) delirium - assessment, prevention, and management, (e) early mobility and exercise, and (f) family engagement and empowerment [31].

Another integrated approach algorithm for critically ill patients targeted the prevention of early deep sedation in the ICU as a risk factor for poor long-term outcomes, including mortality and neurocognitive disorders [32]. Flexible multimodal analgesia, with the minimal use of opioids, is the main concept of this algorithm, together with the use of the lowest doses of sedatives that are still efficient [32]. Promoting sleep, early mobilization, and improved communication of patients with medical personnel and caregivers are also included in the eCASH (early Comfort using Analgesia, minimal Sedatives, and maximal Human care) model as methods to avoid isolation, delirium, and a decreased quality of life [32].

Figure 2: Case management in patients with delirium in clinical populations


Validated tools for measuring delirium symptoms
•CAM
•CAM-ICU
•4-AT
•NEECHAM Confusion Scale
•OSLA
•Daily assessment of delirium is recommended
Therapeutic recommendations
•Treating precipitating factors
•Approaching predisposing factors
•ABCDE(F) protocol
•Multicomponent strategy
•Pharmacological interventions
•Dexmedetomidine- for ICU patients
•ChEI- not supported by evidence
•Benzodiazepine- strictly for delirium due to alcohol/benzodiazepine withdrawal
•Antipsychotics- low-dose, short-term treatment
Prophylactic recommendations
•Flexible minimal analgesia
•Promoting sleep and early mobilisation
•eCASH model
Therapeutic guidelines
•APA Guideline for the treatment of delirium (2010)
•Danish National Clinical Guideline for Prevention and Treatment of Organic Delirium (2021)
•National Institute for Health and Excellence Guideline for the Management of Delirium (2023)

APA= American Psychiatric Association, CAM= Confusion Assessment Method, ChEI= cholinesterase inhibitors, eCASH= early Comfort using Analgesia, minimal Sedatives and maximal Human care, ICU= Intensive Care Unit, NEECHAM= Neelon and Champagne, OSLA= Observational Scale of Level of Arousal

The multi-component strategy for delirium in the elderly includes six intervention directions, i.e., cognitive deficits, sleep deprivation, immobility, visual deficits, hearing impairments, and dehydration [33,34]. Early psychomotor and cognitive action may reduce the duration of delirium in critically ill patients [35].

Methods may be specific to the identified causal factors, such as the treatment of alcohol withdrawal, Wernicke encephalopathy, acute kidney injury, hepatic encephalopathy, diabetic ketoacidosis, etc. [36-40]. Exploring neurological disorders that may represent vulnerability factors for the onset of delirium is an important step in the prophylaxis of these patients [14,41,43]. In patients with neurocognitive disorders due to Alzheimer's disease, Parkinson's disease, or vascular diseases, the initiation of acetylcholinesterase inhibitors (AChEI) may help in reducing the risk of delirium onset/recurrence or its severity [44,45].

Dexmedetomidine was associated with an improved diagnosis for patients with delirium and mechanical ventilation admitted to ICUs [29]. Dexmedetomidine combined with analgesics may reduce the duration of delirium in patients with agitated forms of confusional states [29]. Dexmedetonimide is usually administered in the ICU for adult patients who require a level of sedation that allows for awakening as a response to verbal stimulation, meaning a Richmond Agitation and Sedation Scale (RASS) score between 0 and -3 [46]. Dexmedetomidine is administered by infusion and requires continuous monitoring of the blood pressure, cardiac rhythm, and respiratory functioning [46].

Impairment of cholinergic neurotransmission by high levels of circulating proinflammatory cytokines is considered a critical contributor to the onset of delirium; therefore, the administration of pharmacological agents that increase acetylcholine may be an adequate method to prevent or treat confusional episodes [47,48]. Following this line of reasoning, cholinesterase inhibitors (ChEI) were explored as symptomatic treatments for delirium, independent of the presumed pathophysiological substrate. However, a systematic review found only one study matching the inclusion/exclusion criteria (N=15 participants, out of which 7 have comorbid dementia) did not find a significant difference between rivastigmine and placebo regarding the duration of delirium, adverse events, use of rescue medication, mortality, and study discontinuation [49].

Benzodiazepines are used in cases of delirium due to withdrawal of substances in patients with substance use disorders, and where antipsychotics are contraindicated [29,50]. SAT, which is one of the core elements of the ABCDEF bundle previously mentioned, refers to the need to use a daily discontinuation strategy of sedatives or a continuous titration of these drugs in order to preserve the minimum level of sedation [31].

Antipsychotics are associated with variable results in this population. Based on the results of a meta-analysis and systematic review (n=5 randomized controlled trials, N=1750 patients), the use of antipsychotics in critically ill adults with delirium did not increase the

number of days without delirium or coma vs. placebo and did not show a significant effect on mortality, duration of mechanical ventilation, ICU stay or hospital length [51]. Another meta-analysis (n=19 studies) focused on the prevention and treatment of delirium by using antipsychotics showed these agents had no significant effect on delirium incidence, duration, severity, or ICU length of stay [52]. Yet another systematic review (n=14 sources) showed that uncontrolled studies reflect limited support for the use of low-dose, short-term treatment of delirium with several antipsychotics [53].

APA Guidelines for the Treatment of Delirium (2010) recommends (1) a close collaboration between the psychiatrist and other physicians to ensure appropriate care for these patients; (2) identify the precipitants; (3) initiate interventions for acute conditions; (4) provide disorder-specific treatment for co-occurring diseases; (5) monitor and ensure the safety of the patient; (6) assessment and monitoring of the psychiatric status; (7) assessment of individual and family psychosocial and social characteristics; (8) maintain the therapeutic alliance with the patient and his/her family; (9) education of the patient and family regarding the illness; (10) provide post-delirium management [54]. Environmental interventions, structuring and ensuring support for the patient, and support and education for the family are the most important non-pharmacological interventions, while antipsychotics (orally or intramuscularly, low doses, and for the shortest time needed), benzodiazepines (but there are only limited data, except for the treatment of delirium related to alcohol or benzodiazepine withdrawal), pro-cholinergic drugs (but there is a risk for cholinergic adverse events), vitamins (in specific cases, such as patients with hemodialysis, or alcohol use disorder), morphine or other opiates (in palliative care, and there is a risk of exacerbating the delirium) are considered the most important pharmacological strategies for the management of delirium [54].

The Danish National Clinical Guideline for Prevention and Treatment of Organic Delirium (2021) recommends non-pharmacological therapy to be initiated in all patients with a risk of delirium and in those with delirium (i.e., sensory optimization, orientation and cognitive stimulation, mobilization, nutrition, rehydration, supporting the circadian rhythm) [55]. Placing the delirious patient in a protected environment, actively involving relatives in the treatment of patients with delirium, and constantly reviewing medication for all these patients (i.e., adjusting, including stopping non-essential drugs), and avoiding routinely using antipsychotics for all delirious patients are also recommended by this guideline [55]. Benzodiazepines should not be used in this population except for palliative patients with agitation and terminal delirium or for patients in ICU where respiratory support and monitoring are accessible [55]. Melatonin is not considered by the Danish guidelines a useful intervention, but electroconvulsive therapy may be recommended in refractory cases where other therapeutic options have failed [55].

The National Institute for Health and Excellence (NICE) guideline for the management of delirium (updated January 2023) recommends, for the prevention of delirium, a multi-component approach conducted by a multidisciplinary team, addressing the cognitive impairment and/or disorientation by environmental measures, and address all potential triggers for confusion [56]. Treating delirium involves management of the underlying causes, ensuring communication and reorientation, de-escalation of the situation using verbal and non-verbal techniques, followed, if necessary, by short-term haloperidol, and, if there is still little or no improvement, re-evaluation of the potential precipitants and vulnerability factors, dementia included [56].

Case management for patients with delirium superimposed on a major neurocognitive disorder

The distribution of the sources retrieved during the literature search for the case management of patients with delirium overimposed on MND was similar to that mentioned in the previous section for delirium in clinical populations, and the results are synthetically represented in Figure 3.

Diagnostic aspects of delirium in patients with MND

Regarding the diagnosis aspects, an analysis of the potential biomarkers for delirium superimposed on MND showed that genetic, epigenetic, and pharmacogenetic variables might be used in the near future to construct personalized case management for these patients [57].

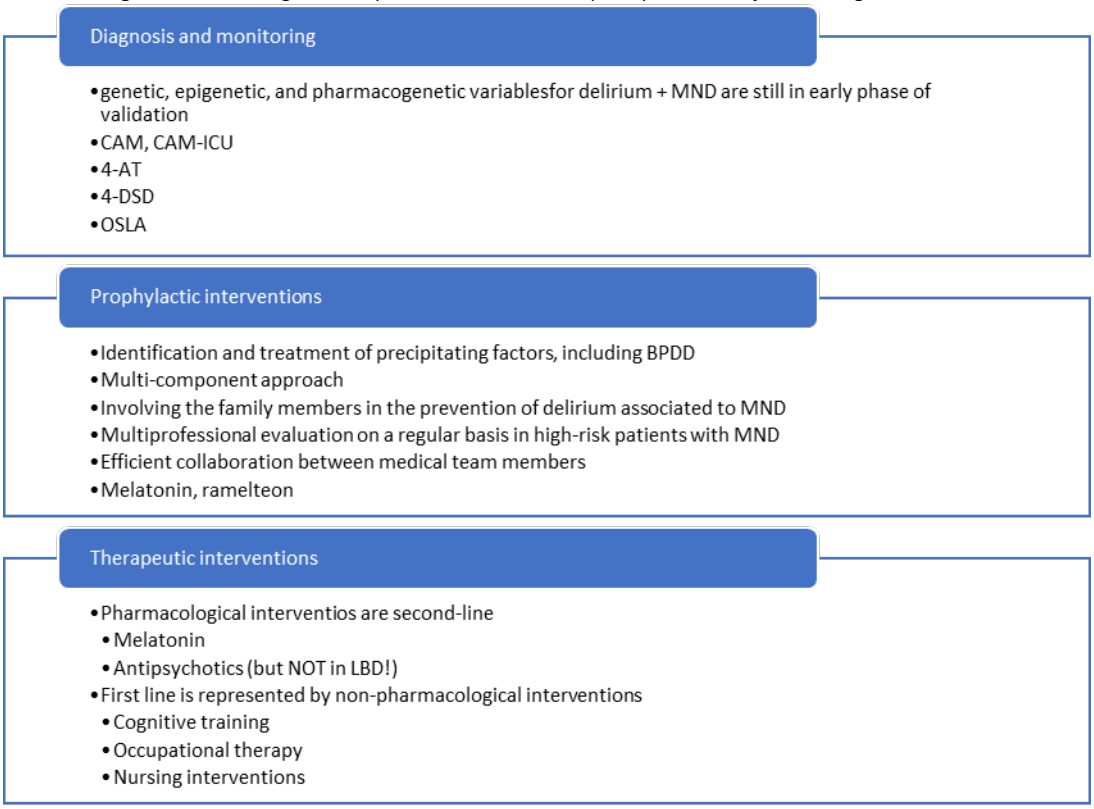
Gene-gene, protein-protein, gene-drug, and gene-miRNA interactions have been detected as potentially significant in this specific population, with several essential genes, like BDNF (brain-derived neurotrophic factor), APP (amyloid beta precursor protein), DNMT1 (DNA methyltransferase 1), APOE (apolipoprotein E), and TNF (tumor necrosis factor) presenting gene x drugs interactions also relevant for this pathology [57]. However, there is no single independent, validated biomarker for delirium, which leaves, for now, at least, the diagnosis to the clinicians [58].

A review dedicated to the best tools for identifying delirium in patients with MND concluded there is no concordance between validated diagnostic criteria, psychometric instruments, and therapeutic guidelines, which makes it difficult for clinicians to identify and treat this pathology appropriately [59]. Taking into account such limitations, CAM and CAM-ICU are the most recommended instruments for the diagnosis of delirium in dementia, based on the review of clinical studies [21,59]. Other instruments, such as 4-AT or 4-DSD (Delirium superimposed on dementia), have also been studied in this population, but there is less data to support their clinical use [59]. The 4-AT may be beneficial for the correct and timely detection of delirium in this population because it can help in the exclusion of cognitive impairments in emergency rooms and hospital admissions [33]. Therefore, as a screening tool, 4-AT is a helpful instrument that requires little time for administration.

The 4-DSD has four items and is derived from 4-AT, but the scoring algorithm is different, and several items have a changed content compared to the initial tool [59]. This instrument assesses the level of alertness, altered brain function, attention integrity, and acute change and fluctuation in mental status [59].

The use of the OSLA in combination with another very simple attention test (that requires the patient to identify a certain letter in a sequence) correctly identified more than 90% of the cases of delirium superimposed on dementia [33,60].

Figure 3: Case management of patients with delirium superimposed on major neurocognitive disorder


Diagnosis and monitoring
•genetic, epigenetic, and pharmacogenetic variablesfor delirium + MND are still in early phase of validation
•CAM, CAM-ICU
•4-AT
•4-DSD
•OSLA
Prophylactic interventions
•Identification and treatment of precipitating factors, including BPDD
•Multi-component approach
•Involving the family members in the prevention of delirium associated to MND
•Multiprofessional evaluation on a regular basis in high-risk patients with MND
•Efficient collaboration between medical team members
•Melatonin, ramelteon
Therapeutic interventions
•Pharmacological interventios are second-line
•Melatonin
•Antipsychotics (but NOT in LBD!)
•First line is represented by non-pharmacological interventions
•Cognitive training
•Occupational therapy
•Nursing interventions

BPDD= behavioral and psychological disturbances in dementia, CAM= Confusion Assessment Method, DSD= Delirium Superimposed on Dementia, ICU= Intensive Care Unit, LBD+ Lewy body dementia, MND= major neurocognitive disorder, OSLA= Observational Scale of Level of Arousal

Preventative and treatment-focused recommendations in patients with delirium and MND

Mentioning that there is no „gold standard" for the diagnosis and treatment of delirium in patients with MND, a systematic review showed that a multi-professional evaluation regularly of high-risk patients with MND is recommended as a step toward the prevention of delirium [61]. An efficient collaboration between multiple members is also needed within the team, which is involved in case management [61]. Eliminating the risk factors for delirium in this vulnerable population is essential [61]. Screening for all the major causes of delirium in patients with MND is strongly recommended and could have significant benefits [33]. Constipation, medications with central nervous system adverse events, infections, vascular factors, electrolytic imbalance, low mobility, malnutrition, pain, incorrect sleep hygiene, and urinary retention should be screened for in patients with MND and sudden clouding sensorium [33].

A non-pharmacological approach is initially indicated in all individuals presenting delirium and MND, based on decreasing the number of medications used, maximization of family support, orienting techniques, adequate hydration, and correction of visual and hearing deficits, whenever possible [21]. However, the controlled studies did not show a consistent effect of environmental strategies in preventing delirium in patients with MND [21].

Pharmacological therapies are considered second-line interventions and applied only when non-pharmacological strategies have failed or are insufficient [61]. The use of melatonin and antipsychotics to treat delirium in MND is not supported enough by evidence [62].

As for the prevention of delirium, the identification of the precipitants and their treatment, initiation of multicomponent interventions, prevention of complications, and monitoring the resolution of the core symptoms are the main directions of case management in patients with delirium and MND [58,62]. The participation of the family members is strongly encouraged by the case managers because the evolution of the patients is often unpredictable even after hospital discharge, and caregivers may play an important role in re-orienting a confused individual by offering him or her a point of reference [58]. Re-assessment of precipitating and vulnerability factors is the first step, and only after that can non-pharmacological and pharmacological treatment be considered [62].

Special care should be given to patients with MND and BPDD, a sub-population that is more vulnerable to the onset of delirium than patients with dementia but without BPDD [63]. The recovery of delirium is slower in patients with both dementia and BPDD; therefore,

identifying early signs of delirium, like sleep impairments, mood lability, and psychomotor agitation, should trigger increased attention and more intensive monitoring [63].

Cognitive training was explored as a possible intervention for MND, to facilitate neuroplasticity in these patients [64]. Based on several similar cognitive features between dementia and MND, the use of recreational activities to enhance attentional abilities and offer cognitive stimulation was suggested to reduce delirium severity and duration, improving quality of life and reducing healthcare costs [64]. A pilot study dedicated to this intervention (N=16 participants) demonstrated a greater decrease in physical function and mental status during the 30 days of monitoring vs. the control group [65]. Delirium, but also the severity of delirium and attention had a trend toward significance in the study vs. control group [65].

Occupational therapy, based on preliminary evidence, can be another option for patients with delirium and MND [66]. A case series (N=6 patients with dual disorders) reported positive results of occupational therapy conducted twice daily for a total of 40 minutes until the delirium was remitted [66].

Nursing interventions for delirium over-imposed on MND were associated with good results [67]. A 10-step intervention was reported to help in the dissolution of delirium in a patient with Alzheimer's dementia: interdisciplinary communication with care providers, reduction of medications administered, communicating calmly and slowly with the patient, avoidance of physical restraints, re-hydration, regulation of the sleep-wake cycles, assess and prompt treatment of pain, education of the family and encouraging family members to participate in care, mobilize the patient as soon as possible, and regulation of the excretory function [67].

Melatonin and ramelteon may be recommended in older patients for the prevention of delirium when admitted to an acute geriatric facility [68,69]. According to the results of a multicenter, randomized study (N=67 patients admitted in ICUs), ramelteon administered nightly was associated with a lower risk of delirium, even after controlling the risk factors, vs. placebo [69].

Antipsychotics are frequently used in clinical practice for this population, but a trial with these medications should be recommended only for a short time, in low doses, and under careful supervision [33]. Special care should be taken when administering antipsychotics in patients with MND due to Parkinson's disease or Lewy Body Dementia [33].

DISCUSSION

The existing evidence reviewed in the previous chapter supports the use of validated instruments for (1) screening in vulnerable populations, patients with MND included; (2) supporting the clinical diagnosis of delirium in the absence of validated biomarkers; (3) monitoring the evolution of delirium during treatment, until the complete resolution of its symptoms [22-26, 33,61]. Also, preventative measures could be applied in vulnerable populations, which may lead to a reduction in the risk of delirium onset, i.e., treating risk factors, close assessment of the clinical status, multi-component interventions, and even limited data supporting pharmacological interventions for short periods of time [58,62,63]. Therapeutic measures that can be initiated in cases of delirium superimposed on MND are mainly non-pharmacological since, for the pharmacological agents, there is only limited data to support their use [29,33,46-50,53-56].

Limitations of this review are related to its narrative nature, and, as a result, not all significant sources may have been found and reviewed. Also, due to the narrative character of the review, no quality of data was assessed, and all sources were treated equally. Finally, there is a paucity of data derived from good-quality trials focused on delirium overimposed on MND, which limits the validity of the review's results, since most data are extrapolated from studies with patients presenting delirium in the clinical population, regardless of the causal factors.

The strengths of the present review are related to the enlarged focus on both pharmacological and non-pharmacological components of case management and the integration of structured assessment instruments into the clinical practice in vulnerable populations.

Future directions of research should include better-quality trials with homogenous populations, e.g., delirium with onset in patients with MND due to Alzheimer's disease, or the prevention of delirium in patients with MND due to Parkinson's disease, but also active comparators and placebo for the pharmacological trials, and a large number of participants with long-period of follow-up, in order to assess the risk of recurrence.

CONCLUSION

When formulating the case management plan for patients with delirium superimposed on MND, the clinician should take into account (1) the need for a multidisciplinary team since the precipitating and vulnerability factors may be complex and have intricate relationships; (2) regularly and frequently assess the patient using instruments like CAM, 4-AT, OSLA, or 4-DSD; (3) include the family in the monitoring of the patients, whenever possible; (4) non-pharmacological interventions, such as cognitive training and occupational therapy, nursing techniques, multi-component approaches, are first-line strategies; (5) pharmacological interventions are considered second-line, and they are administered only for short time and low doses; (6) prophylaxis of delirium in vulnerable populations, MND patients included, remains the single most important way to reduce the complications associated with this pathology.

Conflicts of interest and sources of funding

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Authors' contribution

Conceptualization, O.V., M.M., A.G.M., B.M.P, A.M.C., C.A.S, and C.A.P.; methodology, M.M.M, O.V., A.M.C., C.A.S., and C.A.P; software, O.V..; validation, O.V., C.A.C., A.M.C., C.A.S., and C.A.P..; formal analysis, O.V., M.M.; investigation, O.V., M.M., A.G.M, B.P., M.M.M., A.M.C., and C.A.P..; resources, C.A.P., C.A.S., M.M., O.V..; data curation, O.V., M.M.; writing—original draft preparation, O.V..; writing—review and editing, M.M., C.A.S., A.M.C., C.A.P.; visualization, O.V..; supervision, O.V., C.A.P.; project administration, O.V., M.M. All authors have read and agreed to the published version of the manuscript

Ethics approval and consent to participate

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ORIGINAL ARTICLE

Gender-Dependent Associations Between Digit Ratio and Genetic Polymorphisms, BMI, and Reproductive Factors

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Abstract: The digit ratio (2D:4D) has been associated with prenatal hormonal influences and various traits and pathologies. This article explores the relationship between 2D:4D and a series of common polymorphisms and Torque Teno Viruses. In this study, 120 healthy participants were included. The IGF2 Apa I, ACE I/D, INS -23 Hph I, VDR Fok I, VDR Apa I, VDR Taq I, AT1R A1166C polymorphism were genotyped by PCR-RFLP technique, and the IL-6 -174 G/C polymorphism by tetra-primer ARMS-PCR. The presence of TTV was identified by a hemi-nested PCR technique. Haplotype analyses were performed using the SHEsis software. The average 2D:4D values were similar for men and women. Overweight men presented higher 2D4D ratios than normal-weight women ($p<0.05$). Lower 2D:4D values were recorded in women with pregnancy loss or one child or none ($p<0.001$). Men with lower 2D4D ratios reported a higher number of children ($p<0.001$). The IGF2 GG and ACE DD were associated with a higher digit ratio in all subjects and in the women's subset. A significant association was found in men between 2D:4D and the INS-23 Hph I – IGF2 Apa I T-G haplotype ($p<0.01$). The data obtained in this study indicate a sexual dimorphism for the digit ratio. The associations between 2D:4D and the genetic polymorphisms studied could be influenced by gender.

Keywords: 2D:4D, Insulin-IGF2 haplotype, ACE I/D, parity, BMI

INTRODUCTION

The ratio between the length of second and fourth digits (2D:4D) is determined prenatally, and remains stable throughout life, serving as a marker of early maternal hormonal influences [1,2]. This length is influenced by the ratio between testosterone and estrogen during the fetal period. A smaller digit ratio has been associated with a higher concentration of fetal testosterone and a lower concentration of fetal estrogen [3]. Additionally, the 2D4D ratio can be influenced by the density of receptors for testosterone and estrogen, which is greater for 4D than 2D [2], and also by the maternal environment [4]. Nevertheless, testosterone production during the first years of life could influence secondary sexual differences developing before puberty as 2D4D ratio [4]. Furthermore, the digit ratio was correlated with specific genetic particularities of the child such as a polymorphism in the androgen receptor gene [5]. Therefore, lower digit ratios are common in males whereas higher values are identified in females [6].

The study of the digit ratio offers a compelling gateway into understanding the intricate interplay of genetic, hormonal, and environmental factors from the intrauterine environment. These interactions also may shape an individual's predisposition for different physiological (e.g. height, weight, BMI, athletic performance, reproductive success) [7,8,9,10] or psychological traits (e.g. academic performance) [11]. In addition, the 2D:4D has been associated with various categories of pathologies, ranging from autoimmune diseases (e.g. vitiligo [12], thyroid disease [13]), metabolic disorders [14], and malignant tumors [15] to mental disorders such as autism, ADHD, and depression [16]. A series of polymorphisms such as Insulin, IGF2, angiotensin I-converting enzyme (ACE), angiotensin II type 1

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receptor (AT1R), vitamin D receptor (VDR), and IL-6 genes may imply fetal growth and development and have been associated with some of these pathologies [17,18,19].

Insulin-like growth factor two (IGF2) is a key protein regulating growth, secreted, mostly via the placenta, and after birth by hepatocytes [20]. INS-23Hhp influences IGF2 transcription in the human placenta and it may be implicated in insulin-regulated intrauterine growth and insulin secretion in adults [21].

ACE, a zinc metallopeptidase, plays a pivotal role in the renin-angiotensin-aldosterone system (RAAS), responsible for homeostasis, blood pressure regulation, and water balance in the body. ACE I/D polymorphism has been associated with different pathologies, including pregnancy complications and infertility [22]. Angiotensin II type 1 receptor (AT1R) is a well-reported biomarker for hypertension and AT1R A1166C was strongly associated with the risk of developing pregnancy-induced hypertension [23].

Vitamin D (VD) is a molecule involved in regulating various processes, including phosphate and calcium metabolism, bone mineral density, and immune response [24], but also plays an important role in fetal development. Low maternal VD levels during pregnancy are associated with various adverse obstetric outcomes, such as gestational diabetes mellitus [25]. Vitamin D, as cortisol and sex hormones are all derived from cholesterol, creating an intricate network of interactions. Cortisol and testosterone concentrations might be influenced by vitamin D [26] through the activity of the vitamin D receptor, which is present in Leydig cells [27] (that plays a role in testosterone synthesis) and regulates the activity of the adrenal gland [28] (to produce cortisol). Therefore, three of the most studied VDR polymorphisms may be of interest: VDR Fok I (C/T), VDR ApaI (A/C), and VDR Taq I (C/T). Additionally, a low cortisol reactivity was associated with a low digit ratio [29]. Nevertheless, no significant association between 2D:4D and vitamin D has been reported in the literature so far.

Having pro-inflammatory and anti-inflammatory properties, interleukin 6 (IL-6) plays a major contribution in modulating the immune response, being reported as a biomarker of inflammation and intraamniotic infection [30]. Moreover, IL-6 was associated with right 2D:4D in girls, suggesting that the gender of the subjects and the hand's position in the sagittal plane influence the correlation between IL-6 and digit ratio [31]. The synthesis of pro-inflammatory cytokines, including IL-6, may be influenced by Torque Teno viruses (TTV) [32]. TTV are non-enveloped viruses that belong to the Anelloviridae family that are widespread globally [33]. They have multiple transmission routes, including transplacental transmission, which may have implications in prenatal development, although studies are not consistent on this matter [34, 35]. TTV may represent a potential biomarker of immune function and for some diseases [36].

This article aims to investigate the associations between digit ratio, gender, certain characteristics (such as height, weight, BMI, and reproductive success), and a series of common polymorphisms.

MATERIALS AND METHODS

Selection of subjects.

This study included 120 healthy, unrelated, volunteers (61 women, 59 men), aged between 42 and 60 years (52.73 ± 3.6 years). All participants were informed about the purpose of the study. Selection criteria for the participants included alcohol intake and smoking. Alcohol intake consisted of no more than two standard drinks a day for men and one standard drink a day for women. A beverage is considered alcoholic if it contains up to 10 g of ethanol, according to the World Health Organization [37]. As for smoking, the threshold was 20 cigarettes per day, based on the participants' answers.

Methods and Protocols.

The length between the second digit and the fourth digit was measured by the caliper three times, therefore the value obtained is the average of these three consecutive measurements. It was measured on the ventral surface of the left hand, from a midpoint on the metacarpophalangeal flexion crease to the tip of the digit. The measurements were considered valid if the difference between the maximum and minimum values measured for a finger was less than 5 mm. If the difference was greater, the measurement process was repeated for that participant. The analysis was restricted to subjects with a digit ratio range of 0.96-1.005, with more extreme values excluded.

A peripheral blood sample (300 mL) was collected from each subject in an EDTA tube and genomic DNA was extracted using the Promega Wizard® Genomic DNA Purification Kit. The presence of TTV was identified using a hemi-nested PCR protocol [38]. The ACE I/D polymorphism (rs1799752) was identified by PCR with a primer set for insertion [39], while the PCR-RFLP technique was used for genotyping the polymorphisms IGF2 Apa I (820 G/A, rs680) [40], INS -23 Hph I (-23 A/T, rs689) [41], AT1R A1166C (rs5186) [42], VDR Fok I (C/T, rs2228570), VDR Apa I (A/C, rs7975232), VDR Taq I (C/T rs731236) [43, 44]. IL-6 -174 G/C (rs1800795) was genotyped by the tetra-primer ARMS-PCR technique [45]. Restriction products were resolved by electrophoresis.

Statistical Analysis.

The distribution of qualitative data in subgroups of subjects was analyzed with Chi-square or Fisher tests. The outlier values for 2D:4D were considered values that exceed the mean value ±3 standard deviations. The quantitative values were analyzed using ANOVA, one-way ANOVA with post-hoc Tukey HSD test. Simple linear regression analyses were used to assess the variation in anthropometric parameters with variation in 2D:4D. The statistical analyses were performed using the R Studio software, version 2023.12.1.+402. Haplotype analyses were performed using the SHEsis software [46]. Differences were considered statistically significant if $p<0.05$.

RESULTS

The average age (52.73 ± 3.6; 42-60), weight (71.71±5.06; 63-86), height (1.70±0.02; 1.65-1.75) and BMI (24.96±1.78; 21.89-29.41) and 2D/4D (0.9858 ±0.01; 0.97-1.01) of subjects were estimated. The characteristics of the investigated subjects are presented in Table 1.

We have identified no outliers for 2D:4D in the case of men or women investigated in this study. Men have a higher digit ratio than women, but this difference was not statistically significant (0.9871 vs 0.9845, p >0.05).

Table 1: Characteristics of subjects

Characteristics	Values
Male / Female	59 /61
Age: men vs women	52.89 vs 52.57
Weight: men vs women	74.10 vs 69.39[b]
Height: men vs women	1.70 vs 1.69
BMI: men vs women	25.72 vs 24.21[b]
Smokers: men vs women	24 vs 17
Alcohol drinkers: men vs women	12 vs 3[a]
2D/4D: men vs women	0.9871±0.007 (0.97-0.998) vs 0.9845 ±0.009 (0.97-1.005)
TTV positive samples: men vs women	45 vs 39
INS -23 Hph I: AA/AT/TT	49/66/5
IGF2 Apa: GG/GA/AA	55/57/8
VDR Fok I: CC/CT/TT	53/50/17
VDR Apa I: AA/AC/CC	41/53/26
VDR Taq I: TT/TC/CC	25/52/43
ACE I/D: II/ID/DD	35/52/33
AT1R A1166C: AA/AC/CC	57/48/15
IL-6 -174G/C: GG/GC/CC	75/38/7

[a] p<0.05; [b] p<0.0001

The IGF2 GG and ACE DD were associated with a higher digit ratio in all subjects and also in women (Table 2). No other genotype shows a significant association with the digit ratio.

Table 2: Characteristics associated with 2D:4D

Subgroup compared	2D: 4D average (interval)
All: IGF2 GG vs. (GA+AA)	0.9877±0.0074 (0.97-1.002) vs 0.9841±0.008 (0.97-1.005)[b]
Women: IGF2 GG vs (GA+AA)	0.9873±0.007 (0.97-1.002) vs 0.9823±0.009 (0.97-1.005)[a]
Men: IGF2 GG vs (GA+AA)	0.9881±0.006 (0.973-0.998) vs 0.9861±0.006 (0.97-0.997)
All: ACE DD vs. II	0.9893±0.007 (0.97-1.002) vs 0.9843±0.009 (0.97-1.005)[b]
Women: ACE DD vs. II	0.9899±0,008 (0.97-1,002) vs 0.9811±0.009 (0.97-1.005)[c]
Men: ACE DD vs. II	0.9885±0.005 (0.98-0.996) vs 0.9878±0.007 (0.97- 0.998)
All: ACE (DD+ID) vs II	0.9844±0.008 (0.97-1.005) 0.9843±0.009 (0.97-1.005)
Women: ACE (DD+ID) vs I	0.9823±0.008 (0.97-1.005) vs 0.9811±0.009 (0.97-1.005)
Men: ACE (DD+ID) vs ACE II	0.9866±0.007 (0.97-0.998) vs 0.9877±0.007 (0.973-0.998)

[a] p<0.05; [b] p<0.01; [c] p =0.006

The INS and IGF2 (11p15.5) polymorphisms or VDR (12q13.11) polymorphisms were mapped in close proximity. As a consequence, we evaluated the effects of Ins -23 Hph - IGF2 Apa I and VDR Fok I – Apa I – Taq I haplotypes on 2D:4D. The INS-23 Hph I – IGF2 Apa I T-G haplotype was found to be significantly associated with 2D:4D in men (p<0.01), but not in women (p>0.05). No statistical associations were identified between the digit ratio and VDR Fok I – Apa I – Taq I haplotypes (Table 3).

Twenty-four (39.34%) women reported at least a pregnancy loss. The 2D:4D value of these women was lower compared to those who did not report such an event (0.9799 vs 0.9876, p<0.001). The height in these subsets of women was similar (1.691 vs 1.697, p<0.05) (Figure 1). The average age at which they had their first child was similar between those who had one child and those who had multiple

children (22.93 vs 22.2, p>0.05).

The 2D:4D values were lower in women who had no children compared to those who had children (p <0.001), who had at least two children (p <0.001), or one child (0.9809 vs 0.9865, p < 0.3). In the case of men, the differences identified were significant between men who had at least two children and those who had one child (p<0.001) or who did not have children (p<0.02). In the subset of subjects who did not have children, the lowest average 2D:4D values were recorded in men compared to women (0.9883 vs 0.9809, p< 0.001). The height of men and women stratified by the number of children did not show any statistically significant differences (Figure 2).

Table 3: Association of INS-IGF2 and of VDR haplotypes with 2D:4D

Polymorphisms	Haplotypes	The total count in women's sublot	The total count in men's sublot
VDR Fok I – Apa I – Taq I	CAC	34	31
	TCT	20	7
	CCT	18	24
	TAC	15	22
	CAT	15	7
	CCC	13	14
	TCC	5	4
	TAT	-	9
INS -23Hph I – IGF2 Apa	AG	51	49
	TG	34	33[a]
	AA	35	29
	TA	-	7

(Haplotypes with frequency <0.03 were not taken into consideration; [a] p <0.01)

Figure 1: Analysis of 2D:4D ratio and number of children by gender

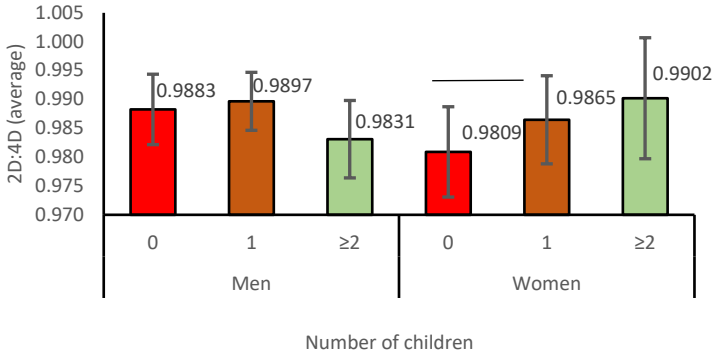
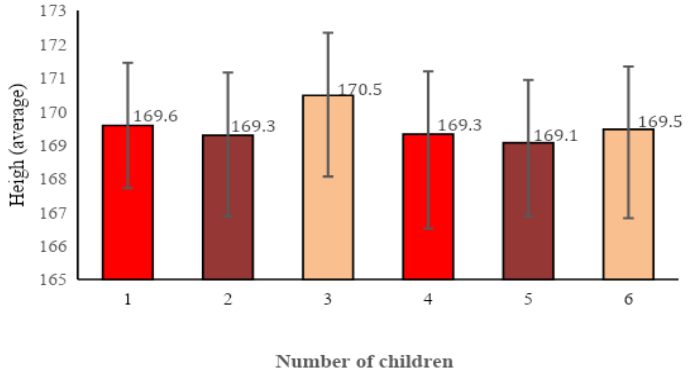


Figure 2: Analysis of height and number of children by gender



The 2D:4D values were higher in overweight subjects than in normal-weight participants (0.984 vs 0.988, p<0.008). The weight (74.1 vs 69.39 kg, p<0.0001) and BMI (25.72 vs 24.21 kg/m^2, p<0.0001), but not height (170 vs 169 cm, p>0.05), were significantly higher in men compared to women. Each gender was subsequently stratified according to BMI into normal-weight and overweight subgroups. There was only a significant difference between the 2D:4D values of overweight men and normal-weight women (0.9884 vs 0.9837,

p<0.05). No significant results were found when the male and female subsets were stratified according to height.

There appears to be a positive correlation between 2D:4D and BMI, regardless of gender (F=0.02) (Figure 3), and an inverse correlation between the 2D:4D and height of men (F = 0.03) (Figure 4). However, the proportion of 2D:4D variance that may be predicted based on BMI (R2=0.047) or height (R2 =0.08) appears to be weak.

The tested genetic polymorphisms were not associated with the height or BMI of men and women (p>0.05). These variables were similar in women stratified by parity.

Figure 3: Linear regression for 2D:4D and BMI (both genders)

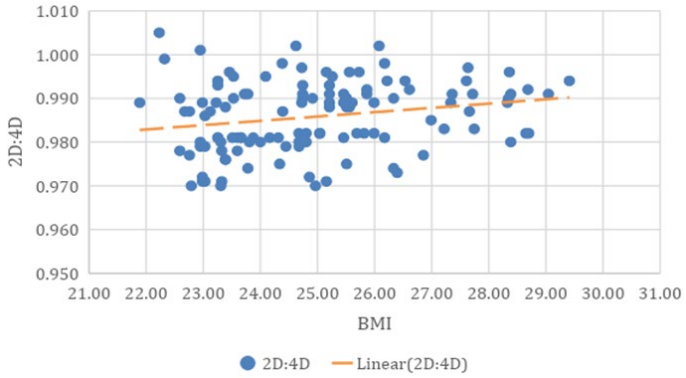
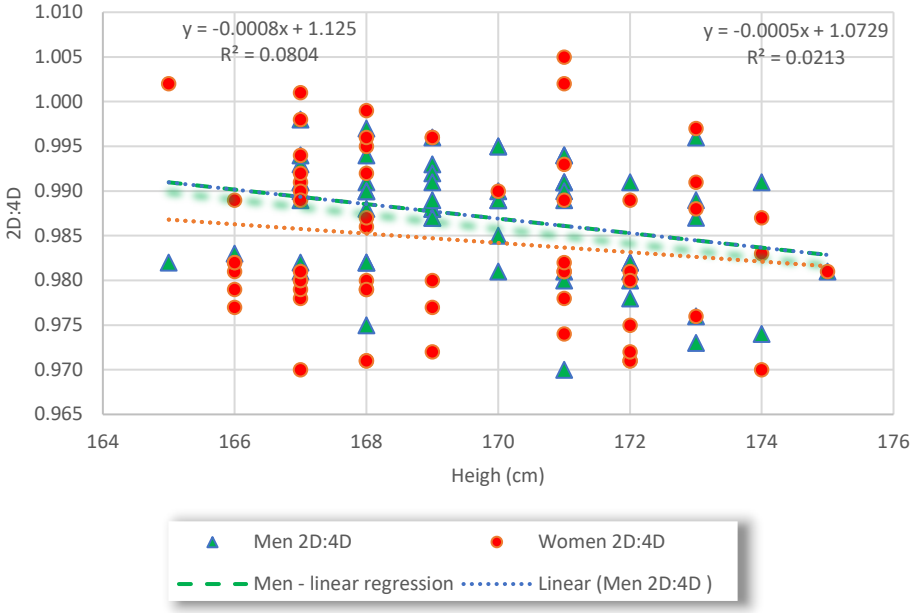


Figure 4: Linear regression for 2D:4D and height of men and women



DISCUSSION

The digit ratio is determined during the prenatal period and in general remains stable throughout life [1]. A study that analyzed the 2D:4D ratio in 327 deceased fetuses (14 to 42 weeks old) concluded that the values were lower than those reported for children and adults in both sexes, suggesting 2D:4D could increase after birth [48]. In addition, a study has shown that this ratio can change, to a significantly reduced extent, during childhood, between the ages of one and five years [47]. Therefore, age may influence to some extent the length between the index and ring fingers. In the present study, the 2D:4D values were not correlated with age, neither at the level of the entire group of adult participants nor at the subgroup level by gender.

The difference between genders appears to be moderated by the type of finger length measurement and by the hand that was measured. Some studies suggest that there are greater differences between genders when measurements are taken on the right hand, which would better reflect prenatal hormone exposure [49,50]. In our sample, measurements were taken on the left hand, for which we obtained higher average values in men than in women, but the differences were not significant (0.9871 vs 0.9845, p >0.05). This result is contrary to the results reported by other studies [3,4]. In a meta-analysis that studied the representation of women in politics and was based on data collected in an online survey, the reported data for Romania indicated higher values in women than in

men for both the left hand (1 vs. 0.985) and the right hand (0.997 vs. 0.986) [50].

In contrast to the 2D:4D, height, weight, and BMI are characteristics that change postnatally, influenced by both genetic and environmental factors. Weak correlations between 2D:4D and these variables were identified in this study. Studies are not consistent on this matter. For example, 2D:4D was positively related to BMI in a very large sample of adults [51]. On the contrary, other studies have reported no significant correlations between these variables and 2D:4D [52,53].

The analysis of anthropometric data we performed showed that the values for weight and BMI were higher in men than in women. Moreover, we identified a significant difference between the 2D:4D values of overweight men and normal-weight women (0.9884 vs 0.9837, $p<0.05$). In the literature, significant positive correlations have been reported between higher (feminized) digit ratios and postnatal parameters (body weight, BMI, and waist and hip circumference) [54,55]. There were no statistically significant differences between height of men and women ($p>0.05$). The linear regression showed a negative correlation between 2D:4D and the height for males ($F = 0.03$), but not for females or both genders. One study reported that body height was negatively correlated with right- and left-hand digit ratios and the correlations were significant for the left-hand digit ratio in men and for the right-hand digit ratio in women [7].

Our data suggested a significant association between 2D:4D and reproductive success which is influenced by gender. Thus, lower average 2D:4D values were recorded in women who reported a pregnancy loss or who had no or one child ($p <0.001$). In the case of men lower 2D:4D values were associated with a higher number of children. Our results are in agreement with some results reported previously in the literature [9,10].

The minor allele frequencies for IGF2 Apa I (MAF A: 0.3 vs. 0.24) [56, 57] and ACE I/D (D: 0.49 vs 0.51) [58] in our lot are consistent with those previously reported in the Romanian population. Previous studies have reported that the IGF2 G allele may contribute to weight gain and eating disorders, and BMI [59]. Another study, which investigated multiple single nucleotide polymorphisms in the IGF2 gene region, concluded that IGF2 genetic variation is a significant determinant of body weight in middle-aged males [60]. The data we have obtained suggest that nearby genes, IGF2 or Insulin, could influence the digit ratio. The IGF2 GG genotype was associated with a higher digit ratio, especially in women ($p<0.05$) whereas the Insulin - IGF2 T-G haplotype was significantly associated with 2D:4D, but only in men. The closely linked IGF2 and Insulin genes have been previously associated with various conditions such as obesity, diabetes, metabolic syndrome, and coronary heart disease [61, 62]. Genetic imprinting influences IGF2 expression [63] and the association between the parent-of-origin allele and various phenotypes. The design of our study did not permit the investigation of IGF2 parent-of-origin.

ACE converts angiotensin I into angiotensin II and most of its functions are mediated by AT1R. ACE D was associated with a higher enzymatic activity of ACE [64]. Carriers of ACE DD have higher values of 2D:4D than ACE II in our lot of subjects ($p<0.01$) and especially in women ($p<0.01$). In a previous study, it was also reported that ACE DD individuals have higher 2D:4D than carriers of ACE II [65]. ACE I/D was also associated with various diseases, such as cardiovascular diseases and hypertension [66] or physical endurance or competitiveness [67]. The association may bias the results we have detected in our healthy subjects. Given the fact that ACE I/D polymorphism and 2D:4D ratio might play a role in cardiovascular pathology, our subjects (42-60 years old), although clinically healthy, may still have a predisposition to develop these diseases. This predisposition might influence the results obtained in this study, potentially causing a bias. The results could also be affected by the small number of subjects included in the study (n=120), as well as by measurement errors related to the length between the index and ring fingers.

Although no significant association was identified between the digit ratio and Torque Teno viruses, the high prevalence of TTV in the population was confirmed, being present in 70% of the subjects included in the study, in line with previously obtained results [32,68].

CONCLUSION

In our dataset, the digit ratio was similar in men and women. The data obtained in this study indicated that INS - IGF2 T-G haplotype, ACE I/D, pregnancy loss, number of children, and BMI are associated with digit ratio. These relations could be also influenced by the gender of the subject. Additional studies are needed to bring new data regarding the relationships between 2D:4D and the genetic polymorphisms of anthropometric characteristics to see if the results we obtained in this study could be replicated. This data could contribute to a broader understanding of how genetics can shape developmental outcomes through prenatal hormones.

Conflicts of interest and sources of funding

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results. This study was funded by the Ministry of Research and Education, grant number PN 23 01 03 03.

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Authors' contribution

Conceptualization, N.S., R.S., R.M., and D.C.; methodology, O.C.; software, R.M. and M.T.; validation, M.I.N., M.L.C., and C.I.; formal analysis, M.T and M.I.N.; investigation, N.S., D.C., L.B., O.A.; resources, L.B., D.C.; data curation, S.R. and O.A..; writing—original draft preparation, N.S., E.S., R.M, O.C.; writing—review and editing, D.C., M.T, I.R., M.L.C.; visualization, M.T.; supervision, D.C. and O.C.; project administration, L.B, and D.C.; funding acquisition, L.B. and S.R.. All authors have read and agreed to the published version of the manuscript

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the National Research and Development Institute for Food Bioresources – IBA Bucharest (protocol code 285/20.03.2023).

Patient consent for publication

Informed consent was obtained from all subjects involved in the study.

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To ensure fast peer review and publication, manuscripts that do not adhere to the following instructions will be returned to the corresponding author for technical revision before undergoing peer review. Note that submission implies that the content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium. Once you have prepared your submission following the Guidelines, manuscripts should be submitted online at office@rjmm.ro.

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Aims and Scope

Romanian Journal of Military Medicine (RJMM) is the official journal of the Romanian Association of Military Physicians. The Journal publishes peer-reviewed original papers, reviews, meta-analyses, systematic reviews, and editorials concerned with clinical practice and research in the fields of medicine. Papers may cover the medical, surgical, radiological, pathological, biochemical, physiological, ethical, and historical subject areas. Clinical trials are afforded expedited publication if deemed suitable. RJMM also deals with the basic sciences and experimental work, particularly that with clear relevance to disease mechanisms and new therapies. Case reports and letters to the Editor may not be considered for publication.

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The acceptance criteria for all papers and reviews are based on the quality and originality of the research and its clinical and scientific significance to our readership. All manuscripts are peer-reviewed under the direction of an Academic Editor. The Editor-in-Chief reserves the right to refuse any material for review that does not conform to the submission guidelines detailed throughout this document, including ethical issues, completion of an Exclusive License Form, and stipulations as to length.

ETHICAL CONSIDERATIONS

Principles for Publication of Research Involving Human Subjects

Manuscripts must contain a statement to the effect that all human studies have been reviewed by the appropriate ethics committee and have therefore been performed following the ethical standards laid down in an appropriate version of the Declaration of Helsinki (as revised in Brazil 2013), available at: http://www.wma.net/en/30publications/10policies/b3/index.html. It should also state clearly in the text that all persons gave their informed consent before their inclusion in the study. Details that might disclose the identity of the subjects under the study should be omitted. Photographs need to be cropped sufficiently to prevent human subjects from being recognized (or an eye bar should be used).

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We strongly recommend, as a condition of consideration for publication, registration in a public trials registry. Trials register at or before the onset of patient enrolment. This policy applies to any clinical trial. We define a clinical trial as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Studies designed for other purposes, such as to study pharmacokinetics or major toxicity (e.g., phase 1 trials) are exempt.

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These are invited by the Editor-in-Chief or their delegated editor and should be a brief review of the subject concerned, with reference to and commentary about one or more articles published in the same issue of RJMM. Editorials are generally 1200–1500 words, may contain one table or figure, and cite up to 15 references, including the source article. This should be cited as Rom. J. Mil. Med. (year); (vol): [issue].

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The Editors welcome contributions to the Education and Imaging section. The purpose is to present imaging for the evaluation of unusual features of common conditions or diagnosis of unusual cases. Contributions will be reviewed by the Executive Editors. The format of the Images pages involves two parts, each of which will occupy up to one journal page. In Part 1, a case will be described briefly, including a summary of the presentation, clinical features, and key laboratory results. One to two key images will then be presented. It is helpful to the reader if the author responds to questions that follow from the images of the case, such as 'What is your diagnosis? What are the features indicated on the CT scan? What is the differential diagnosis?' Part 2 will briefly describe the imaging features, particularly those that lead to a diagnosis or are critical for management. Differential diagnosis should be mentioned. It will be useful to include either further images or pathological details that validate the imaging diagnosis. Occasionally, the presentation of analogous cases or related images from a similar case might be appropriate.

Please include between one and three references to definitive studies and appropriate reviews of the subject. The format of the Images page involves a brief background and description of the disorder of interest together with two figures of high quality. Colored photographs are encouraged. The submission may take the form of a case report or may illustrate particular features from more than one patient.

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Acknowledgments

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